Sixth Report of the Director, National Heart, Lung, and Blood Institute

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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February 21, 1979

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

February 21, 1979

The President
The White House
Washington, D.C.

Dear Mr. President:

I am submitting to you the Sixth Report of the Director, National Heart, Lung, and Blood Institute. The Report outlines our progress over the past year, and our plan for the next five years. In addition, selected accomplishments and highlights of 1978 research projects are presented, as are some of the 1978 accomplishments of special NHLBI programs such as the Specialized Centers of Research, clinical trials, Research and Demonstration Centers, and prevention, education and control programs. Programs of manpower development, interagency coordination and international activities are described as well.

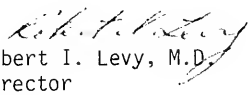
Although we are all encouraged that there has been a sharp decline in cardiovascular disease death rates over the last 10 years, cardiovascular diseases still caused over half of all deaths in 1976 and accounted for more than one-third of all potential years-of-life lost as a result of illness.

The social and economic burden of diseases of the lungs and respiratory system is also severe. While these diseases cause fewer deaths than cardiovascular diseases, they can kill earlier in life and account for more than five percent of all the potential years-of-life lost as a result of illness. In 1975, treatment costs alone for lung and related diseases amounted to seven and one-half billion dollars. Since blood diseases so frequently strike during childhood, standard economic measures cannot fully reflect the loss or costs in terms of suffering and grief. These diseases, including the hemoglobinopathies, are the cause or complication of a variety of serious disorders.

To capitalize on the achieved progress, the Institute will continue to pursue research activities in all areas of the biomedical research spectrum; the development and validation of new knowledge concerning fundamental aspects of life processes, and the etiology and pathogenesis of specific diseases; better approaches to disease prevention and improved means of controlling diseases and their complications; and the expeditious and appropriate translation of research results into practical health care.

We feel confident that these efforts will add the necessary momentum to continue the success of the past six years, in responding to the challenge of reducing not only morbidity and mortality but also the substantial economic costs of these diseases.

Sincerely,



Robert I. Levy, M.D.
Director

Preface

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 called for a coordinated national effort to reduce the suffering, death, and disability caused by cardiovascular, pulmonary, and blood diseases. The legislation directed the National Heart, Lung, and Blood Institute (NHLBI) to plan and implement a national program of research to combat these diseases.

The *Sixth Report of the Director of the National Heart, Lung, and Blood Institute* examines the accomplishments of the Institute during the past year and projects the needs and goals for the coming year. Included in this year's report are descriptions of the magnitude of the problems facing the Institute and the Nation, a description of the Institute's programs directed at solving these problems, a brief overview of NHLBI's planning and evaluation process, and an explanation of the strategy and range of research activities that characterize NHLBI's approach to improving knowledge of the causes, possible treatment and prevention of heart, lung, and blood diseases. Selected accomplishments and highlights of 1978 research projects are presented, as are some of the 1978 accomplishments of special NHLBI programs such as the Specialized Centers of Research, clinical trials, Research and Demonstration Centers, and prevention, education and control programs. Programs of manpower development, interagency coordination and international activities are described as well. An individual section is devoted to setting forth goals and planned activities for 1979 through 1983, and a section on resource allocations indicates the fiscal and personnel requirements to carry out activities planned for 1979 as well as projections through 1983.

The 1978 Director's report is necessarily more modest in scope than last year's report, which reviewed the state of the science and programs for the previous 5 years and projected program goals for the next 5 years. This report reviews events of the past year and clarifies NHLBI plans for the next 5 years.

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I.
Magnitude of the Problem

The NHLBI has primary responsibility for the scientific investigation of heart, blood vessel, lung and blood diseases as well as the management of our Nation's blood resources. Diseases of the heart, lung, and blood account for an inordinately large share of the sickness, death, and financial loss caused by illness, and the magnitude of NHLBI's responsibilities must be viewed in the light of this burden.

Heart disease has been the foremost cause of death in the United States for several decades. Despite the fact that there has been a steady decline in cardiovascular disease death rates since the 1950's, cardiovascular diseases still caused almost half of all deaths in 1976 (see table I) and accounted for more than one-third of all potential years of life lost to illness (see table II). Cardiovascular disorders rank second only to respiratory disease as the primary reason for visits to physicians. Even more alarming is the fact that cardiovascular disorders are the greatest single cause of permanent disability as reflected by Social Security disability statistics in the United States. Heart disease,

Table I

Ten Leading Causes of Death in the United States, 1976

	Deaths	Percent of Total Deaths
Heart Disease	723,878	37.5
Cancer	377,312	19.6
Stroke	188,623	9.8
Accidents	100,761	5.2
Influenza-Pneumonia	61,866	3.2
Lung Diseases*	43,907	2.3
Diabetes	34,508	1.8
Cirrhosis of the Liver	31,453	1.6
Arteriosclerosis**	29,366	1.5
Suicide	26,832	1.4
Total	1,618,506	83.9
Other Deaths	310,032	16.1
Total Deaths	1,928,538	100.0

* Chronic Obstructive Pulmonary Diseases
** Not Otherwise Specified

Source: Monthly Vital Statistics Report, June 1977

Table II

Years of Life Lost According to Disease Category of Underlying Cause of Death, USA, 1974

ICD Category	Years of Life Lost	Percent of Total
Diseases of the circulatory system	12,034,328	36.6
Neoplasms	5,885,065	17.9
Accidents, poisonings, and violence	5,618,129	17.1
Diseases of the respiratory system	1,672,336	5.1
Diseases of the digestive system	1,398,025	4.3
Congenital anomalies	850,785	2.6
Endocrine, nutritional, and metabolic diseases	689,889	2.1
Diseases of the nervous system and sense organs	480,761	1.5
Infective and parasitic diseases	422,922	1.3
Diseases of the genitourinary system	349,311	1.0
Mental disorders	239,115	.7
Diseases of the blood and blood-forming organs	110,292	.3
Diseases of the musculoskeletal system and connective tissue	89,801	.3
Diseases of the skin and subcutaneous tissue	30,825	.1
Pregnancy, childbirth, and the puerperium	21,575	.1
Other	2,960,591	9.0
Total	32,853,750	100.0

Derived from: Dorothy P. Rice *et al.* "The Current Burden of Illness in the United States." National Academy of Sciences, Washington, D.C., October 1976

in particular, often causes long periods of limited activity and accounts for more bed days than any other condition. The economic burden of cardiovascular disorders is exceptionally high (table III). On the whole, heart and blood vessel diseases cause the greatest share of the financial burden of illness, constituting about one-fifth of the total cost of illness in this country.

The social and economic burden of diseases of the lungs and respiratory system is also severe. While these diseases caused fewer deaths than cardiovascular diseases during 1975, they killed earlier in life and caused more than 5.1 percent of the years of life lost to illness. Even more striking is the huge toll these diseases exacted in sickness, treatment requirements, and lost work days. Respiratory diseases are the greatest cause of people's seeking a physician's attention, accounting for more than 20 percent of all physician contacts and 12 percent of all short-term hospital stays. There are more lost work days from respiratory disorders than any other category of illness. In 1975, over 135 million work days were lost to respiratory illness—nearly 30 percent of the total days of work lost. While treatment costs for lung and related diseases are only about half those for cardiovascular diseases, they still amounted to $7.5 billion in 1975. In that year, the combined costs of treatment, sickness, and early death from respiratory disorders were estimated to have exceeded $19 billion, or 8 percent of the total economic burden imposed by all illnesses.

The tragedy of blood diseases is especially evident in that they often kill early in life, childhood bleeding disorders being one example. This and other blood diseases so frequently strike during childhood that standard economic measures cannot fully reflect the loss or costs in terms of suffering and grief.

Table III

Economic Cost of Selected Diseases, 1975 (dollars in millions)

Diagnosis	Direct Costs		Indirect Costs: Morbidity		Indirect Costs: Mortality		Combined Costs	
	$	%	$	%	$	%	$	%
Diseases of the Circulatory System	15,999	16.1	8,735	15.1	25,674	29.2	50,408	20.0
Diseases of the Respiratory System	7,552	7.6	8,561	14.8	3,605	4.1	19,718	8.0
Diseases of the Blood and Blood Forming Organs	696	.7	289	.5	264	.3	1,249	1.0
Circulatory, Respiratory, and Blood Diseases Combined	24,247	24.4	17,585	30.4	29,543	33.6	71,375	29.0
All Diseases	99,374	100.0	57,846	100.0	87,926	100.0	244,246	100.0

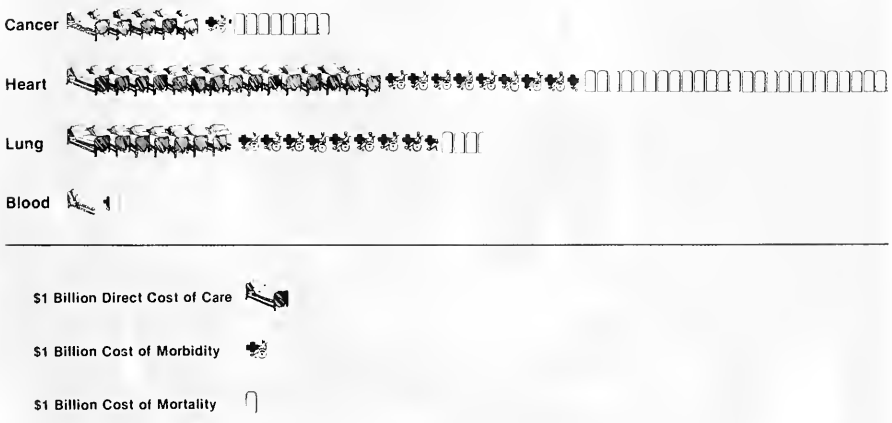
Source: Dorothy P. Rice *et al.* "The Current Burden of Illness in the United States." National Academy of Sciences, Washington, D.C., October 1976.

The American people incur appalling financial losses because of heart, lung, and blood diseases. The combined costs of medical treatment alone for these disorders were over $24 billion in 1975, amounting to nearly 25 percent of all United States treatment costs. The economic loss due to morbidity was over $17 billion, and losses due to early death cost Americans nearly $30 billion. Overall, the economic burden of heart, lung, and blood diseases exceeded $70 billion and accounted for approximately 29 percent of the total U.S. economic cost of illness. Table III summarizes data concerning the economic cost of heart, lung, and blood diseases, and figure 1 gives a graphic representation of the economic costs of cancer, heart, lung, and blood diseases.

Economic costs for these diseases help place different health problems and national needs in perspective, but financial and statistical data alone cannot reflect the full social impact of heart, lung, and blood diseases. The personal loss involved in the death of a loved one cannot be described by statistics. The death of a child, the grief of family members, the pain and despair of a permanently disabled person cannot be quantified. Obviously, early death and lost productivity have a seriously debilitating effect on the community. And the need to expend scarce resources on medical care precludes using those same resources for other worthy ends. But the potential that we all lose when a promising young person dies, when a vital adult is stricken, goes beyond measurement.

Figure 1

Direct Cost and Costs of Morbidity and Mortality for Cancer, Heart, Lung, and Blood Diseases



Derived from: Dorothy P. Rice et al., "The Current Burden of Illness in the United States," National Academy of Sciences, Washington, D.C., October 1976.

II.
National Program Description

LEGISLATION AND ORGANIZATION

In response to the severity of national health problems and the need for research to improve health conditions, the NHLBI has grown over the last three decades. The National Heart Institute was established in 1948 under the authority of the National Heart Act (P.L. 80-655). In its early years the National Heart Institute initiated and supported basic programs to uncover the mechanisms of the cardiovascular diseases and to develop means to prevent and control them. During ensuing years, the Institute expanded and improved on these efforts. The Institute's mandate was enlarged in 1969 to encompass research and training in respiratory diseases, and its name was changed to the National Heart and Lung Institute.

In 1972, with the passage of Public Law 92-423, Congress directed development of a plan to address the problems of heart, blood vessel, lung, and blood diseases. The law specified that NHLBI was to plan and coordinate the attack on these diseases by developing a national program. During the last 6 years, this Program has become complex, and truly national in scope and impact. The Program involves many disciplines and organizations, and encompasses the full spectrum of biomedical research from basic laboratory studies through applied clinical research and its application to clinical practice.

Congress reaffirmed its support of NHLBI's program with the Health Research and Health Services Amendments of 1976 (P.L. 92-278). These amendments continued National Program efforts in heart, lung, and blood disease and added expanded responsibilities for research in blood, blood products, and the management of our Nation's blood resources. The legislation also renamed the Institute the National

NHLBI intramural scientists conduct research in highly sophisticated facilities such as this anaerobic laboratory in which investigators can conduct experiments in an oxygen-free environment.

Heart, Lung, and Blood Institute. Under the legislation, the primary missions of NHLBI are to:

- Conduct and support research to increase fundamental and clinical knowledge about the cardiovascular, pulmonary and blood systems, and blood resources.
- Develop new and improved techniques for preventing, diagnosing, and treating diseases affecting these systems.
- Carry out clinical testing and evaluate new knowledge and techniques which show promise of improving prevention, diagnosis, and therapy.
- Support the training of scientists, clinicians, and teachers in the cardiovascular, pulmonary, and blood fields.
- Conduct a comprehensive program of education and demonstrations to inform the general public and health professionals about research and clinical advances related to Institute programs.

With changes in legislative authorization, the Institute's programs have grown, and its organizational structure has been adjusted to respond to increased responsibilities. Based on the 1972 Act and 1976 Amendments, NHLBI is presently organized into three major extramural program divisions for research related to cardiovascular diseases, lung diseases, and blood diseases and resources. Responsibility for the 20 program elements in the National Heart, Blood Vessel, Lung, and Blood Program is divided among these divisions as outlined in table IV. In addition, the Division of Intramural Research is responsible for the Institute's active intramural research program.

Table IV

National Program Elements by Division

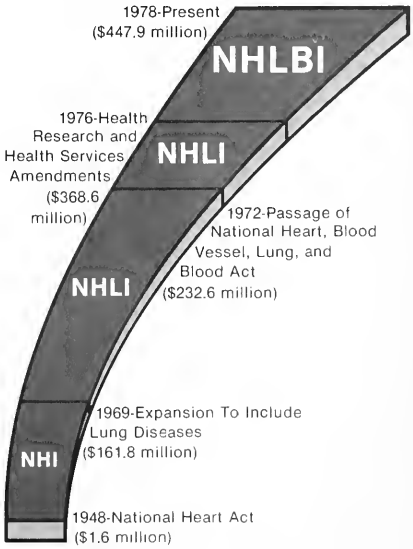
Heart and Vascular Diseases	Lung Diseases	Blood Diseases and Resources
Arteriosclerosis	Structure and Function of the Lung	Bleeding and Clotting Disorders
Hypertension	Emphysema and Chronic Bronchitis	Red Blood Cell Disorders
Cerebrovascular Disease	Pediatric Pulmonary Disease	Sickle Cell Disease
Coronary Heart Disease	Fibrotic and Immunologic Lung Diseases	Blood Resources
Peripheral Vascular Disease	Respiratory Failure	
Arrhythmias	Pulmonary Vascular Diseases	
Heart Failure and Shock		
Congenital and Rheumatic Heart Diseases		
Cardiomyopathies and Infections of the Heart		
Circulatory Assistance		

The amount and allocation of the budget have also changed noticeably during the Institute's history. In 1948, the first budget for the National Heart Institute was $1.6 million; in 1972, the National Heart and Lung Institute's budget was $232.6 million; and in 1978, the NHLBI's budget totaled $447.9 million (figure 2).

As the Institute has responded to new research advances and opportunities as well as changing perceptions of national need, the emphasis of Institute programs has also gradually shifted. The process of clinical validation of new treatment methods has increased over the last decade. Furthermore, the Institute emphasis on demonstration, prevention, and control efforts has grown significantly as new authorizations and new basic and clinical research results have warranted.

Figure 2

Growth of NHLBI Budget During the Institute's History



III. Overview of National Program Plan, Strategy, and Planning Process, 1979

NATIONAL PROGRAM PLAN

The National Heart, Lung, and Blood Institute in 1978 marked its 30th anniversary and the sixth year since Congress enlarged the Institute's authority to encompass heart, blood vessel, lung, and blood diseases and blood resources. NHLBI chose that occasion to conduct a major assessment of the Institute's programs, progress, and accomplishments. The *Fifth Report of the Director* reviewed both the 1972 and 1977 state of the science as well as program goals and accomplishments over the intervening years. It also projected program goals and research activities through 1982. The 1978 report of the Director provides an overview of the National Program Plan and Strategy updated in the fifth Director's report as well as an explanation of special emphases developed during the past year. The 1979 to 1983 goals and planned activities for each of the major program elements are specified in the Program Goals and Planned Activities section of this report. The following section summarizes certain unifying themes which cut across the various program emphases, and it explains the strategy and planning process used to develop and implement NHLBI initiatives.

The major thrust of NHLBI activities will be to continue the full range of activities in research, demonstration, prevention, education, control, and training encompassing all phases of the biomedical research spectrum. The National Program will continue to develop knowledge concerning fundamental aspects of life processes, the etiology and pathogenesis of specific diseases, better approaches to preventing disease, and improved means of controlling diseases and their complications, and the timely and appropriate translation of this knowledge into improved health care and health care delivery practices that are effective, safe, and acceptable.

To capitalize on the progress made to date and address the significant problems associated with cardiovascular, pulmonary, and blood diseases and resources, increasing emphasis will be placed on the following areas:

- *Prevention, education, and control* programs will continue to gain in prominence with increased emphasis on the translation of knowledge into health care practice. These programs will focus on application of proven preventive and therapeutic regimens not ony through dissemination of information, but also through efforts to influence health behavior. This latter area is of major importance and includes research on motivation, health behavior, and alternative educational strategies for influencing behavior.

- *Knowledge development* continues to be a critical aspect of the National Program. New approaches to prevention and control will find their origin and development in the fundamental, applied, and clinical research elements of the Institute's research strategy. Major emphasis will continue to be placed on relevant, high-quality, investigator-initiated research.

- *Clinical trials* validate in a carefully controlled setting the potential efficacy and safety of preventive and therapeutic regimens. Special emphasis will continue to be placed on identifying promising regimens ready for testing in a human population and evaluating their efficacy and safety through carefully designed clinical trials.

- *Research in childhood diseases* is expected to receive more emphasis over the next 5 years. Greater recognition that heart, lung, and blood diseases may have their origin in childhood has made the Institute more cognizant of the need to assess opportunities for research in childhood diseases. Several activities are ongoing or planned in this area.

- *Training and manpower development* programs will have high priority over the next several years. A greater demand for highly trained professionals is expected in the immediate future as more complex and sophisticated research approaches and modalities continue to develop. To meet these demands, the Institute will continue to evaluate needs for scientific manpower and initiate new approaches to complement the individual and institutional National Research Service Awards.

NATIONAL PROGRAM STRATEGY

The NHLBI carries out its mission through a balanced national program of research, validation, demonstration, and professional and public education. Prevention offers the greatest promise of reducing death and disability and, thus, is the primary goal of the National Program. Strong emphasis is also placed on controlling the painful and disabling complications of disease and on identifying those who are at high risk of developing diseases in the future.

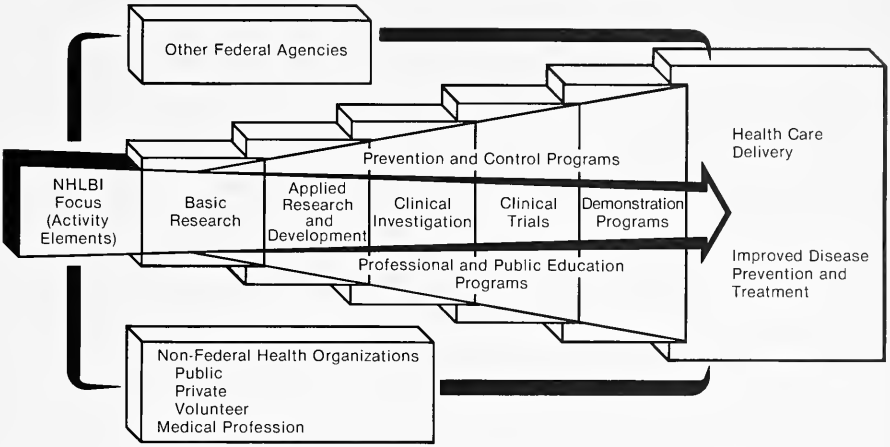
The NHLBI program strategy is directed to maximize the beneficial impact on the public. This approach involves a logical progression of activities through a continuum beginning with basic research on fundamental life processes and mechanisms, and progressing through to practical demonstrations of the clinical applicability of new research findings.

Figure 3 provides a necessarily simplified depiction of this progression. However, in reality the process is complex, dynamic, and interactive. It has overlapping and interdependent phases, significant variation in the individual activities, and involves contributions from diverse organizations and groups throughout the country. Although figure 3 portrays the underlying logic, each medical advance does not necessarily progress through each phase of the process in the order shown. There are many possible entry and exit points, and information concerning efficacy, safety, impact, and other aspects of particular technologies and approaches is continually fed back to earlier phases of the research continuum.

An important aspect of the NHLBI's program strategy is the effort to hasten the progression of new knowledge through the spectrum so that the more effective and safe technologies can be made available to the medical profession and public without undue delay. The Institute has implemented, and will continue to develop, processes and mechanisms to ensure the timely and prudent translation of newly developed proven technology, and to discourage improper use of poorly validated technology by the public and health care community.

The NHLBI conducts a range of activities designed to identify, develop, and promote prompt adoption of approaches which are scientifically valid, socially and ethically acceptable, and economically feasible. This is accomplished through an orderly process of interrelated stages known as the technology transfer process. Figure 4 illustrates the major

Figure 3
The Biomedical Research Spectrum



types of activities, or stages, in this process. In reality, the stages overlap. In particular instances the concrete activities, methods, participants, data and sequence may vary. Nevertheless, the illustrated stages do show the logical sequence of events in the planning process.

The individual stages shown in figure 4 are discussed briefly below:

- *Knowledge development* includes all biomedical, behavioral, and educational research directly related to the Institute's mission. This stage includes basic research, applied research and development, clinical investigations, and clinical trials, as well as the behavioral, motivational, and educational research components of prevention, education, and control programs illustrated in figure 3. Scientific findings are continuously assessed during the research and development phase. Examination of a potentially important technology at this stage will aid in the rapid identification of important, beneficial, and new research knowledge and in the initiation of appropriate steps for technology assessment and transfer to the health care community.

  Formal scientific assessment by the Institute staff and the programmatic advisory committee is a regular part of the Institute's planning process, and is also done as needed, often with the involvement of specialized committees, task forces, and working groups. Identification of a candidate technology for assessment and transfer is a specific assignment of the programmatic advisory committees and Division staff.

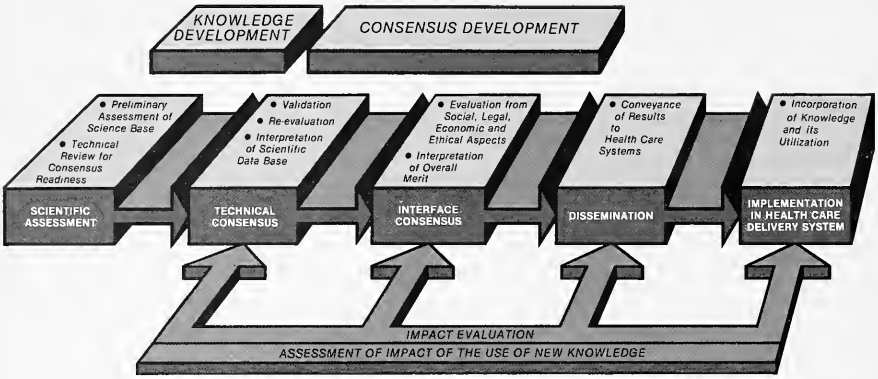
- *Technical consensus development* involves a series of activities to achieve agreement on the scientific facts regarding the indications, safety, and efficacy of a given medical innovation. This stage is more structured and specific than the assessment that occurs during knowledge development. As a preliminary step in the initiation of consensus development, a technical consensus plan is developed by a Division working group composed of Division staff, members of the advisory committee, plus additional individuals as needed. This plan outlines the expected clinical significance of a technology that has been identified as offering a potential improvement in health care. This working group also judges the adequacy and reliability of the data acquired through safety and efficacy testing.

  The working group then makes a preliminary assessment about the need for a full evaluation of cost, ethical, social, or other plausible impacts.

  Experts in a particular field — those in the best position to judge and with the best understanding of the problem—are called togther to carry out the technical consensus plan. They ascertain whether a particular innovation is scientifically reliable and

Figure 4

NHLBI Technology Transfer Process



offers a significant advantage over techniques currently in use. The number of experts invited to participate in NHLBI-sponsored technical consensus development conferences varies from a few to over 100, depending upon the field of science on which the technology in question is based. The NHLBI is intimately involved in this stage through activities ranging from planning and coordination to participation and documentation of recommendations of consensus conferences. Each Division, using the appropriate expert advice from the scientific community and professional societies, is responsible for the planning and design of credible technical consensus conferences in their specific program area. A Division uses task forces, working groups, conferences or workshops to examine the data base and determine those aspects of a technology that could potentially lead to medically significant or cost-effective improvements in health care. Although the circumstances surrounding the development of a technical assessment for a particular technology are unique, *all technical consensus exercises sponsored by the NHLBI address such common elements as: the probable clinical significance of new findings; whether validation for indications, efficacy, and safety has been adequate, and, if not, what additional studies are needed; and the state of readiness for transfer to health practice.*

- *Interface consensus development* embodies a full consideration of the non-scientific factors involved in moving a new technology into the health care delivery system. Results and recommendations emerging from technical assessment and consensus development are blended with health care delivery issues to develop policy, fiscal, and regulatory recommendations, and guidelines for eventual use of the technology by the health care providers. The process brings together those units of the Federal government, the professional and voluntary societies, the manufacturers, the public, and others as appropriate so that all constituencies can appraise the technology in light of the many factors that enter into the delivery of health care. *The recommendations from interface consensus must reflect the interests and views of the health care community, the regulatory agencies, and the general public, as well as the scientists who performed the technical evaluation and developed the knowledge base.*

- *Information dissemination* is essential for technology transfer; it encourages the prompt adoption and appropriate use of modalities receiving favorable recommendations from consensus development exercises, as well as discouraging the utilization of those technologies judged as being impracticable. These activities are carried out primarily through the Institute's prevention, education, and control programs; through Research and Demonstration Centers; and with the aid of the National Library of Medicine. Demonstration programs designed to test methods of introducing or facilitating the delivery of new medical innovations to the public are also included in this stage. A variety of

organizations are involved in the dissemination of information: professional societies, research centers, medical schools, other Federal agencies, and voluntary health agencies.

- *Application,* or utilization, represents the ultimate objective of the process and depends on the effectiveness of information dissemination. These two stages, application and dissemination, are closely related, with the NHLBI assuming a major responsibility for ensuring prompt adoption of new innovations and modalities through demonstration and education programs.

- *Impact evaluation* is an important stage in which the progress of the incorporation of an individual medical innovation into health care is monitored and evaluated with regard to the extent and impact of its application. The results of this evaluation are fed back to earlier stages to ensure periodic reassessment as well as to aid in improving the transfer process. Selected activities in this stage are included in the evaluation plan for the Institute and thus are sponsored by the Office of Program Planning and Evaluation (OPPE) in conjunction with the appropriate Division program.

  Results and recommendations of transfer activities, as well as interim status information, are reported by the staff of a Division to the Office of the Director, NHLBI. Tracking of technology assessment activities sponsored by the NHLBI is the responsibility of a technology transfer coordinator who is based in the OPPE. The coordinator takes responsibility for any special reporting that may be required as a result of interest by the biomedical community, Office for Medical Applications of Research (OMAR); Office of the Director, NIH; the Office of Health Technology (OHT); Office of the Assistant Secretary for Health; the Office of Technology Assessment; and members of the Congress and their staffs.

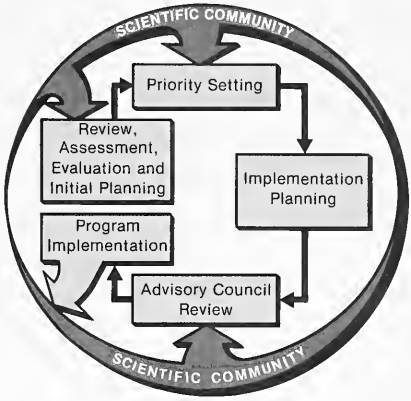
PLANNING, IMPLEMENTATION, AND EVALUATION

The NHLBI utilizes an integrated and continuous process to plan, implement, and evaluate the National Program. This process was established to ensure responsiveness to legislative mandates, identification and pursuit of the most promising opportunities, and the effective use of resources.

The planning, implementation, and evaluation process takes place in a yearly cycle which involves

Figure 5

Steps in the NHLBI Planning Process



a continuous flow of information from the public, the medical community, other Federal agencies, and non-Federal organizations (figure 5). The Institute is responsible for coordinating this flow and converting it into worthwhile programs. The scientific community plays a prominent role through participation on various advisory and review groups, task forces, and working groups involved in assessing progress and determining future directions of the program.

The process can be characterized as systematic and disciplined, while at the same time dynamic and varied in terms of specific approaches. It is designed to ensure a thorough review of the entire program as well as the implementation of new programs and the expansion, modification, or discontinuation of existing programs. This process involves five steps as follows:

- *Review, assessment, evaluation, and initial planning* of programs is done through a review of the goals, objectives, and progress of the five year National Program Plan with respect to the state of the science, as well as the impact of the program on medical care and the health of the public. This is accomplished with the participation of the NHLBI program staff, scientific advisory committees, and members of the general scientific community through workshops, task forces, and technical working groups convened to reach consensus on future directions for the program. The results of special evaluation studies provide important input to this step. The end products of this

step are an update of the five year plan and a preliminary list of program initiatives and recommended program directions for future years, together with revised objectives where appropriate.

- *Priority setting* is the second step in the process, in which proposed new initiatives for implementation in the next year are ranked according to goals and objectives of the National Program, results, progress, and potential impact of ongoing programs, and fiscal and schedule constraints. This is accomplished jointly by the staff of the Institute's categorical divisions and appropriate advisory committees. The product of this step is a set of further defined initiatives, ranked by priority within major program categories.

- *Implementation planning* constitutes the third step, in which the staff of the categorical divisions and the Office of the Director convert the ranked initiatives into specific program plans including programmatic justification, management and fiscal plans, and funding mechanisms. The end product of this step is the preliminary NHLBI Implementation Plan and Program Budget which reflects available resources, legislative mandates and intent, as well as inter-institute and inter-agency responsibilities.

- *Advisory Council review* consists of a thorough review of the Implementation Plan by the full National Heart, Lung, and Blood Advisory Council. Council advice and recommendations are solicited and considered in developing the final NHLBI Implementation Plan and Program Budget.

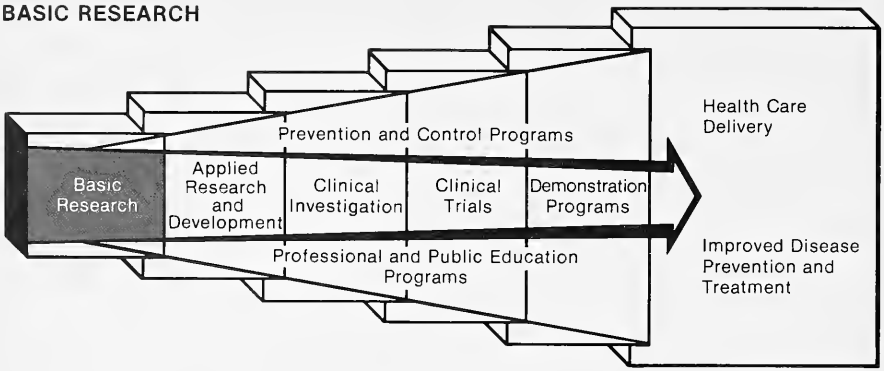
- *Program implementation* consists of translating specific mandates and approved initiatives contained in the Implementation Plan into operational projects. This is a complex process requiring the availability and application of scientific knowledge and resources of all kinds, including scientific manpower, facilities, equipment, and funds. Implementation is carried out through various types of grants and contracts, intramural research, collaboration with other Federal agencies through interagency agreements, as well as jointly supported international activities.

The NHLBI uses these major processes and systems to provide for expedient and effective program planning and implementation. These systems help to ensure appropriate transfer of research advances and provide for scientific validation of new techniques of prevention and treatment. The results of these processes are applied in NHLBI program implementation and are disseminated to the health care community as a whole.

IV. Accomplishments and Highlights

In the past year, there have been significant accomplishments in every area of the biomedical research spectrum. In some instances these accomplishments have immediate applications, and in others the accomplishments add crucial information to a store of knowledge which has been developing over a period of time. Because of the cumulative nature of research breakthroughs, it is especially difficult to identify the most significant accomplishments at a single point in time. Bearing this constraint in mind, NHLBI program staff members have selected certain highlights which they feel represent significant progress. These highlights illustrate the Institute's research program strategy and indicate the scope, diversity, and interdependence of the Institute's programs, and the several elements of the research spectrum presented in figure 3.

Additional highlights of special emphasis programs are presented in the section, Status of Special Program Initiatives. Professional education programs are also further highlighted in the section titled Training and Manpower Development Programs.



Basic research is a systematic, intensive effort directed toward greater knowledge or understanding of the subject studied.

Within biomedicine, basic research deals with the structure and function of molecules, organelles, cells, tissues, organisms, and populations of man — or of suitable nonhuman models — in health and disease.

As the foundation of the Institute's program, basic research on disease etiology and pathogenesis receives the major portion of Institute resources. This research has resulted in a number of significant concepts, theories, and discoveries which, in turn, have become the foundation for further research, refinement, development, evaluation, and dissemination to the medical community and the public.

Atherosclerosis

... *Progress in Understanding the Nature of Blood-Vessel Wall Interactions in the Development of Atherosclerosis*

One current theory of atherogenesis is that some type of injury to the arterial vessel wall results in platelets adhering to the injured area. A series of changes follows, culminating in fibrous, lipid-containing lesions. If these lesions continue to progress, they can severely obstruct the interior of the vessel and thereby lessen blood flow to vital organs.

One current area of atherogenesis investigation is the role of Factor VIII-related-von Willebrand Factor (VIIIR:WF) in platelet-vessel wall interaction and subsequent atherosclerosis. Research on pigs homozygous for von Willebrand's disease (vWd), a hereditary bleeding disorder characterized by a deficiency of VIIIR:WF and decreased platelet stickiness, showed that while over half of the control pigs exhibited multiple atherosclerotic plaques and intimal thickening, none of the pigs with vWd had multiple plaques. In addition, when the pigs were placed on high cholesterol diets for up to 6 months, there was a significant difference in the incidence and extent of the aortic lesions observed. These results suggest that the hemostatic defect in the pigs with vWd may have protected them from spontaneous or induced atherosclerosis.

Furthermore, studies of cultured endothelial cells, which line blood vessel walls, from the vWd pigs have shown abnormal levels of VIIIR:WF and reduced platelet interaction. Cultured human endothelial cells synthesize and release VIIIR:WF, and this protein can be found in subcellular platelet membrane and granule fractions. Decreased adhesion of vWd platelets to the subendothelium has been observed after the introduction of nonanticoagulated blood. Therefore, all evidence suggests that the hemostatic defect in vWd is due to impaired platelet adhesion and that this decreased adhesion may have a negative effect on the development of atherosclerosis. If this theory is correct, it would have significant implications for future research in the pathogenesis and prevention of atherosclerosis.

Atherosclerosis

. . . Reversing the Buildup of Fatty Plaques

The relationship between cholesterol, atherosclerosis, and coronary heart disease has been amply demonstrated in epidemiologic and animal studies. But it has not yet been demonstrated that once atherosclerosis is established in the human coronary arteries, it can be made to regress. Recent animal studies, however, do suggest that at least the first stage, or "fatty" plaques, can be made to regress by controlling the amount of cholesterol in the diet.

Some plaques in humans are believed to undergo a three-stage development. First-stage plaque is "fatty" in nature, second-stage plaque is predominantly fibrous, and end-stage plaque is made of of layers of calcified, necrotic and fibrous material which overarches a lipid core. Earlier studies have found that plaque regression will not begin until plasma cholesterol levels are reduced to the order of 200 mgm/dl. These studies also revealed that the extent of plaque regression is related to the plaque stage of development. Fatty plaques regress more readily than fibrous or end-stage plaques.

A recent study of rhesus monkeys confirms these findings. Animals with induced atherosclerosis were placed on cholesterol-restricted diets. Animals maintained at about 200 mgm/dl had less fatty plaquing than those maintained at 300 mgm/dl. While fatty plaques did regress, there was no apparent regression in the extent of fibrous plaques. While further data will emerge, this work implies that secondary prevention or regression therapy will be most effective before fibrous plaques have developed.

Atherosclerosis

. . . Virus Implicated in the Formation of Experimental Plaques in Chickens

Experiments have demonstrated that Marek's (herpes) virus causes atherosclerosis in chickens. In these studies, pathogen-free animals did not develop atherosclerosis when fed cholesterol, while infected chickens did develop severe plaques without cholesterol feeding. When infected chickens were fed cholesterol, plaque development increased. The virus has been located in the plaques themselves.

Diabetes and Cardiovascular Disease

. . . Relationship Between Diabetes and Cardiovascular Disease Better Understood

Diabetes is a chronic disorder in which a person is unable to metabolize carbohydrates due to the impaired production or activity of the hormone insulin. Diabetes has been identified as a major risk factor in cardiovascular disease. Persons with diabetes are twice as prone to coronary heart disease and stroke, and are five times as prone to arterial diseases of the limbs. While a majority of persons with diabetes can control the acute aspects of their disease, they often incur long-term complications, particularly of the cardiovascular system.

Although cardiovascular diseases and diabetes are assumed to develop independently, there is some probability of an early interaction at the cellular level, since diabetes is known to have a unique pathogenic effect on the capillaries, and diseases of the large vessels are markedly accelerated in persons with diabetes.

Within the last year, several reports have suggested that abnormally high rates of congestive heart failure in adult-onset diabetes are primarily associated with pathogenic deposits of collagen in the muscle tissues of the heart, but juvenile-onset diabetes is associated with early microvascular diseases followed by severe atherosclerosis. The mechanisms by which diabetes affects the metabolism of the artery wall have been examined in experimental animals. Diabetes depresses the activity of the hydrolases, including those contained in the lysosomes. While insulin treatment reverses the depression, the reversal is much slower when diabetes goes untreated for long periods of time.

Transport Phenomena

. . . New Observations Concerning the Regulation of Blood Supply to the Blood Vessel Walls

Understanding the behavior and control of blood vessels remains a critical problem in circulatory phenomena. In the last year, studies have added to our knowledge of factors governing blood supply to the blood vessels.

A recently completed study has produced unique data on the regulation of blood flow through the vasa vasorum (blood supply to the blood vessel walls). The study finds that the vasa vasorum dilates

during intravenous infusion of adenosine and it constricts during hemorrhagic hypotension. The vasa have a layer of smooth muscle which provides the anatomic basis of this response.

Interestingly, in acute hypertension the expected increase in blood flow through the aortic vasa vasorum does not occur. The explanation for this phenomenon is not yet fully understood.

Bronchiolitis

... A New Understanding of Pathogenesis

Little is known about the pathogenesis of bronchiolitis, an acute lower respiratory tract infection in infants and small children. Respiratory syncytial virus appears to be the primary agent causing this disease although other viral agents are also implicated. Some interesting clues to the ways specialized cells are injured by respiratory disease agents were provided by model studies employing tracheal tissues (hamster) in organ culture infected with *Bordetella pertussis*, the organism which causes whooping cough. Electron micoscopic examination of hamster cells exposed to virulent *B. pertussis* revealed that virulent strains attach to and destroy only ciliated cells. They do not attach to or harm other epithelial cells. On the other hand, nonvirulent organisms do not attach to or harm any of the tracheal cells examined. Since the ciliated cells participate in the clearance of mucus and other debris from the lungs and may need several weeks to regenerate, similar damage occurring to the ciliated cells may explain the lengthy course of clinical diseases such as bronchiolitis. Futhermore, the severity of the cellular injury noted in the experimental situation suggests that these bacteria could produce permanent damage leading to chronic airway disease in later life.

Oxygen Toxicity and Endothelial Damage

... New Understanding

Using endothelial regeneration as a marker of injury indicates that oxygen produces endothelial injury both in the alveolar capillaries and in the endothelium of the small pre- and postcapillary vessels as large as 200mm in diameter. The extent of oxygen injury of the lung suggests that oxygen toxicity can reduce the total number of endothelial cells by 47 percent. This extensive destruction of the endothelial surface is surprising. Normally less than 1 percent of the capillary surface area (perhaps as low as 10^6 of 1 percent) is involved in fluid and solute flux. This means that gross edema might be expected with little recognizable endothelial damage. The fact that oxygen causes gross endothelial damage with little edema means that blood flow must be reduced to these grossly damaged capillaries, so that no capillary transport occurs.

Interesting features of acute lung injury with oxygen have been observed by following the cells that divide after the injury has occurred. Studies of this nature have shown that while endothelial cells begin to divide first after oxygen lung injury, epithelial cells soon follow. Data of this type reemphasize the fact that the close structural integrity of the alveolar wall means that both epithelial and endothelial cells are likely to be damaged by most alveolar injuries. The relationship between endothelial injury and the subsequent proliferation of epithelial and interstitial cells, particularly fibroblasts, is of obvious importance and needs to be systematically investigated.

Pulmonary Edema

... Increased Knowledge of Biochemical Mechanisms

Several mediators which produce pulmonary edema either by increasing microvascular pressure or by increasing the permeability of the exchange vessels have been studied in unanesthetized sheep by collection of lung lymph. Using lung lymph flow and its protein concentration as an index of the net fluid and protein flux across the pulmonary exchange vessels, it has been shown that intravenous infusions of PGE_2 or endoperoxides increase lymph flow due to an increase in vascular pressures. On the other hand, intravenous infusion of salicylates, which inhibit PG synthesis, results in an increase in both lymph flow and lymph protein clearance without increasing pulmonary vascular pressure, suggesting that the permeability of the microvascular membrane has been increased. Thus, salicylates may have a direct effect on the microvascular membrane. Prostaglandins, on the other hand, may be necessary for maintaining the integrity of the membrane. The result with salicylates has a direct clinical implication since people with aspirin toxicity develop permeability pulmonary edema.

Lung Cell Culture

. . . New Techniques for Study

It is now well recognized that the lung is a complex cellular organ with as many as 40 different types of cells, each with a specific function and organized in such ways as to facilitate gas exchange in the myriad (300 million) tiny air sacs or alveoli. It is thus of major interest that a special culture environment has been developed to maintain pieces of living (fetal animal) lung tissue for more than 5 months, during which time the major cell types of the alveoli continue to develop and function as normal adult cells. This system provides a novel means for the study of the structure and function of the alveoli in normal and injured lung tissue. The fact that lung explants can be maintained in culture allows observations of cellular function that could not be obtained by studying any one of the 40 cell types in isolation.

Lung Inflammation

. . . Biochemical Findings May Lead to Improved Treatment

Recent research is gradually discovering how inflammatory processes in the lung occur. Anaphylatoxins are chemical substances normally produced in the blood stream when the complement system is activated in response to infections or allergens. If released in large amounts, these chemical mediators can produce anaphylactic reactions — conditions closely resembling allergic shock. A major advance toward understanding the mechanisms of action of this biochemical system has been the elucidation of the complete chemical structure of human anaphylatoxin, C5a. C5a is a major, if not the predominant, serum chemotactic factor responsible for the enhanced white blood cell migration to a site of tissue injury. It is particularly interesting that only a small segment of the C5a molecule is responsible for its anaphylactic activity. Under usual conditions when complement is activated in the blood stream and C5a is formed, it is immediately converted to a form without anaphylactic activity by removal of the terminal arginine. However, the converted C5a still retains its important chemotactic function. This protects us from the serious consequences of circulating anaphylatoxin, while permitting the beneficial stimulation of white blood cells to control inflammation and enhance tissue repair. Currently, synthetic peptide analogues of certain complement derivatives are being prepared as potential tools to aid in preventing allergic reactions and facilitate healing in tissues damaged by a variety of harmful agents.

Lung Control of Physiological Processes

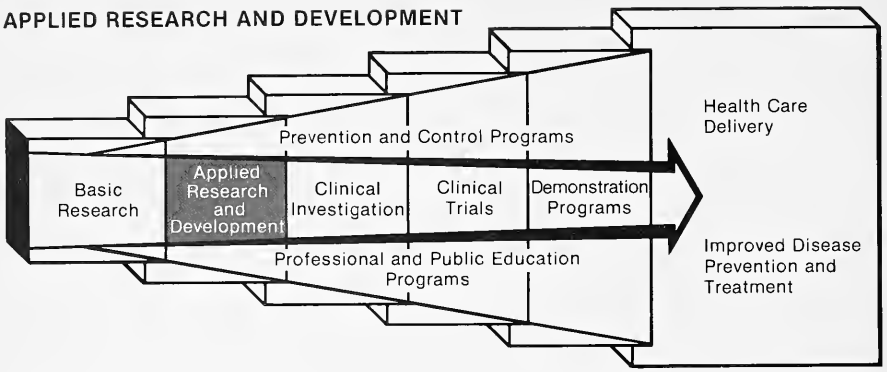
. . . The Role of the Lung in Blood Pressure Regulation

In addition to its role in gas exchange, the lung appears to be an organ which provides remarkable metabolic and endocrine control over the rest of the body. For example, the lung can exert a direct effect on blood pressure, through the action of angiotensin converting enzyme which increases blood pressure by inactivating bradykinin and also by converting angiotensin I to angiotensin II. A major advance in this area has been reported recently. Through the use of antibodies, fluorescent markers, and biochemical assays, the angiotensin converting enzyme has been localized on the innermost surface of lung endothelial cells. This localization has been confirmed in both the intact lung and endothelial cells grown in culture. The definitive localization and characterization of the angiotensin converting enzyme may well have implications for the design of drugs intended to alter the activity of the enzyme, thereby providing insight into the role of the lung in regulation of blood pressure and the possibility of interfering with the regulatory process.

Sickle Cell Disease

. . . Advances in Understanding the Molecular Basis of the Sickling Phenomenon

In sickle cell disease the red corpuscles tend to become deformed ("sickled") in the circulation as the result of an inborn structural abnormality of the hemoglobin, which is called hemoglobin S (HbS), as opposed to normal hemoglobin (HbA). Much has been learned about the structure and function of the HbS molecule, the gel it tends to form, and the sickling red corpuscle. Red cells containing HbS become deformed when their oxygen concentration is abnormally low; the abnormal hemoglobin forms long polymers which bring about a gel-like state and distort the cells into shapes reminiscent of sickles. Recent advances utilizing sophisticated techniques, such as measurements of viscosity, light-scattering techniques, optical birefringence, and nuclear magnetic resonance, have greatly advanced our understanding of the aggregation and polymerization of HbS. A complete understanding of the physicochemical nature of the sickling process may provide ways of modifying the reaction at the molecular level.



Applied research is a systematic study directed toward applying new knowledge to meet a recognized need. In both the laboratory and clinical settings, applied research is aimed first at obtaining specific knowledge that will enable the investigator to judge whether it is feasible to produce a new or improved means of preventing, diagnosing, or treating a particular disease. Subsequently, new approaches and technologies can be developed. To accomplish these goals, applied research is dependent on the existence of a relevant scientific base of knowledge. From this foundation, applied researchers create a means to accomplish a specific practical goal.

Development is the systematic application of available knowledge which is directed toward the production of useful materials, devices, agents, and methods to meet a recognized need. It is a subset of applied research, sharing common goals. Developmental processes to achieve these goals include design, development, and improvement of prototypes and new processes to meet functional or economic requirements.

Atherosclerosis

. . . Noninvasive Means To Characterize Atherosclerotic Lesions in Vessels

Some important forms of treating coronary and other arterial diseases depend on being able to detect blockages of the blood vessels. Once these blockages can be located, measured and characterized, it is often possible to determine appropriate surgical, pharmacologic or other means to reduce the obstruction. Until recently, methods for detecting and analyzing blockages required invasive procedures. However, recent advances have developed a variety of noninvasive diagnostic methods.

Six contract programs are currently developing and evaluating noninvasive diagnostic instrumentation and techniques to image atherosclerotic lesions using ultrasonic methods. Clinical and research applications are being made to carotid and femoral arteries at present, and renal, iliac, and aortic applications will soon be examined.

The prototype instruments are able to image cross-sections of arteries to show the presence and structure of very small lesions, even when blood flow is only minimally obstructed and when acoustic bruits are absent. Early data suggest that the diagnostic accuracy and specificity of the ultrasonic examinations may compare favorably with conventional angiographic techniques.

Ischemia

. . . Protecting Ischemic Myocardium

One of the most promising areas of current research is directed at finding ways to limit infarction (tissue damage) under conditions of ischemia (or decreased blood flow). In recent months increased emphasis has been placed on the study of the basic mechanisms and processes associated with ischemic myocardium and its reversibility or irreversibility. Several studies have advanced this area of investigation.

The influence of the time interval between coronary artery occlusion and the administration of an

apparently beneficial drug such as hyaluronidase has been determined. In animal studies, this intervention is effective in saving ischemic myocardium when administered 20 minutes, 3 hours, and 6 hours following coronary artery occlusion, but is devoid of any protective effect when administered 9 hours after occlusion. Also, the beneficial effect of propranolol in protecting microvascular integrity was demonstrated.

An electron microscope study has demonstrated the beneficial effect of hyaluronidase on the myocytes and the microvasculature and also showed their effect in sparing oxygen. Futhermore, it has been shown that perfusion of an ischemic zone can be improved by vasoconstriction, and as a consequence certain alpha-adrenergic agonists such as methoxamine may reduce ischemic injury by this mechanism.

Other experiments in rabbits have demonstrated that glycolytic blockade is deleterious to ischemic hearts, whereas glycolytic stimulation has beneficial effects. In addition, nitroglycerin infusion has been observed to be effectual in improving ischemic dysfunction.

Studies in dogs have validated the hypothesis that variance in infarct size is caused by variance in coronary collateral blood flow. Nitroglycerin has been found to reduce infarct size, while mannitol is without benefit.

A collaborative clinical trial has been established to assess in man the therapeutic efficacy of propranolol and hyaluronidase administered within 18 hours of the onset of the symptoms of myocardial infarction. A subgroup of patients who received the therapy within 8 hours will be evaluated separately.

Diagnosis and Evaluation

... *Noninvasive Method for Imaging Cross-Sections of the Entire Heart* In Vivo

Results obtained during the past year have demonstrated that it is possible to rapidly measure the extent of heart tissue in jeopardy from ischemia. Externally detectable changes in myocardial metabolism of fatty acids induced by ischemia can be quantified by positron emission transaxial tomography with acquisition of computer-reconstructed images of cross-sections of the entire heart *in vivo* in experimental animals and in patients. Since differentiation between depressed metabolism and irreversible injury is possible with this technique, the approach should permit prompt assessment of the extent of myocardium in jeopardy from ischemia and provide a base line for assessing the effect of interventions designed to reduce the extent of injury.

Hypertension

... *Increased Knowledge of the Relationship Between Hypertension and Psychosocial Stress*

Hypertension and psychosocial stress have been thought to be related for some time, but the precise nature of the biochemical processes that are involved is not fully understood. Psychosocially induced hypertension has been considered to result, in part, from activation of the sympathetic nervous system. However, recent studies in mice have demonstrated that an increase in plasma renin activity may also be a causative factor. Studies also suggest that the degree of psychosocial interaction required to increase renin need not be very great. Moreover, the pattern of changes in plasma renin activity seen with the development of psychosocial hypertension in mice is similar to the changes observed in human essential hypertension (or hypertension that has no identifiable cause). This suggests that the psychosocial hypertension model in mice may be relevant to human hypertension, especially in those instances where hypertension does not have a known biochemical cause.

Heart Failure and Shock

... *The Effect of Anesthetics in Altering the Physiological Response to Hemorrhage and Hypotension*

Hemorrhagic shock is a condition in which either trauma or disease causes bleeding and hypotension, or depressed blood pressure. The loss of blood and decreased blood pressure can lead to decreased blood flow and a lack of sufficient oxygen supply resulting in tissue damage or infarction.

Research is under way concerning the role anesthetics play in altering survival rates, blood flow, and oxygen delivery to tissues during hemorrhage. Findings indicate that there is significantly less anaerobic metabolism during hemorrhagic hypotension in animals anesthetized with ketamine than in those anesthetized with halothane or fluoroxene.

These findings are consistent with previous survival data and histological findings which suggested that ketamine anesthesia is associated with lower mortality and less evidence of tissue hypoxia. This implies that some anesthetic agents are preferable to others when hypovolemia is present or anticipated.

Lung Damage and Pollution

... Early Warning Index and Potential Protective Measures

The lung has a remarkable capacity to repair itself following an abrupt injury such as exposure to toxins including those in polluted air. Through the use of an animal model, the effects of exposure to these toxins have been examined. Results indicate that the machinery for the repair of lung tissue requires 2 to 3 days to be activated; however, the process can be accelerated by drugs such as hydrocortisone. Since several complex biochemical processes are involved in the repair process, it is particularly significant that oxides of nitrogen and ozone, which are present in smog, cause changes in lung metabolism in laboratory animals exposed to concentrations equivalent to those in Los Angeles smog. These metabolic changes may provide an early warning index of injury and may help to determine an "acceptable" level of pollutants.

Chronic Obstructive Lung Disease

... Effects of Pollution and Activity Levels

Pollutants such as ozone are present in high concentrations in the air of urban areas and are thought to be a cause of lung disease. It has been determined that the activity levels of persons in polluted environments may alter their exposure to noxious particles and gases. For example, children, joggers and laborers who exercise frequently have high levels of ventilation and inhale more polluted air. This excess exposure to pollutants may have a detrimental effect. In an experiment designed to examine the relationship of exercise to ozone toxicity, exercising mice exposed to high concentrations of ozone were found to have a mortality rate three times higher than resting mice exposed to the same levels of ozone. The exercising mice were also more likely to develop pulmonary edema, indicative of severe lung injury. Further experiments in dog lungs confirm that changing ventilation patterns as would occur in exercise alters particle deposition patterns in the lungs.

Animal Model of Pulmonary Hypertension

... New Insights into Prenatal Factors

Many individuals have developed hypoxic pulmonary hypertension, or an elevated blood pressure in the lungs, as a result of reduced oxygen in the airways. This occurs at high altitudes and in association with a number of heart and lung diseases. Many animals also develop this disorder, and cattle appear to be particularly susceptible. Even at moderately high mountain altitudes cattle often develop severe hypoxic pulmonary hypertension with right heart failure, a condition known as brisket disease. To adequately study this disease, a breeding program has ultimately led to the development of both resistant and susceptible strains of cattle for use as animal models. Through continued breeding and testing of progeny, the traits for susceptibility and resistance to hypoxic pulmonary hypertension in cattle have been shown to be transmitted from parents to offspring. Although it is most likely that transfer of this trait occurs through genetic mechanisms, the possibility cannot be ruled out that the progeny acquire these traits from their mother's intrauterine environment. Examination of lung tissue surgically removed has indicated that the small arteries of the lung of susceptible progeny are thicker-walled and probably contain more smooth muscle than those of the resistant progeny. Such findings explain why the susceptible cattle show greater hypoxic pulmonary hypertension than the resistant cattle. Like cattle, humans also develop variable pulmonary hypertensive responses to hypoxia, which suggests that some individuals are "susceptible" while others are "resistant." Thus, the cattle model may be useful in determining the basis for susceptibility and resistance to hypoxic hypertension and whether these traits are transmitted genetically or are acquired.

Blood Pressure Regulation in Premature Infants

... A Link with Respiratory Distress Syndrome

Recently, large quantities of bradykinin, a potent depressor of blood pressure, have been detected in the circulation of infants at the time of birth and during cold stress, such as the hypothermia for open heart surgery. These findings may provide an explanation for the abnormally low blood pressures commonly found in infants suffering from respiratory distress

syndrome (RDS). In the premature infant, the autonomic nervous system, a major regulator of blood pressure in older infants and adults, is not yet fully developed. Regulation of blood pressure in the immature infant is dependent on the action of an angiotensin converting enzyme which inactivates bradykinin, raising pressure; the enzyme also is responsible for the conversion of angiotensin I to angiotensin II, which raises blood pressure. Using a newly developed microassay technique, the lungs of immature rabbit fetuses were found to have a strikingly impaired ability to clear bradykinin or to convert angiotensin I to angiotensin II. Furthermore, hypoxia in adult dogs and hypoxia in cultured endothelial cells inhibit the actions of the converting enzyme. This suggests that the effect of hypoxic inhibition on the converting enzyme may have major implications for blood pressure regulation in prematurely born infants who have limited enzyme capacity.

Acoustic Method for Detection of Airway Obstruction

... A Noninvasive Approach

In several lung diseases such as asthma, bronchitis, and emphysema, the airways become obstructed, and ventilation of the alveoli becomes markedly reduced. Recently, an acoustic pulse-response technique, which appears to provide a sensitive measurement of changes in airway caliber, has been developed and tested in animals. This new technique is much like sonar. It involves introducing a pressure wave, which is heard as a sharp "click," into the mouth of a subject. Echoes that come back from the airways are recorded and analyzed by computer to provide an estimate of airway cross-sectional area as a function of distance from the mouth. The method simultaneously provides information on the degree and location of airway obstruction. The method is inexpensive to administer, has no adverse side effects, and requires less than one second to complete. It is now being refined for study in large numbers of animals and humans for potential use as a screening tool.

Shock Lung Syndrome

... A Model for Study

"Shock lung" or "acute respiratory distress syndrome" is a major cause of disability and death in patients following trauma, certain overwhelming infections, acute pancreatitis, and burns. The cause of this sudden deterioration in pulmonary function, which results in high-protein pulmonary edema, is unknown. It now has been shown that all of these underlying diseases activate the complement system of blood and that many of the features of "shock lung," such as plugging of the pulmonary microvasculature with granulocytes and high-protein pulmonary edema, can be reproduced in various animal species by purposely activating the complement system. In addition, the implied pulmonary endothelial damage associated with "shock lung" has been studied using endothelial cell cultures which showed that the endothelial cells are damaged by granulocytes triggered by activated complement components, particularly C5a. This damage is ameliorated by very high doses of corticosteroids in concentrations similar to those used empirically in the treatment of "shock lung" patients. In addition, these same concentrations inhibit granulocyte aggregation *in vitro* and prevent granulocyte plugging of pulmonary vessels in animals in which complement has been activated experimentally. These studies strongly suggest that the "shock lung" syndrome is caused by excessive and prolonged complement activation and that C5a is the trigger of granulocyte-mediated pulmonary damage. The inhibition of these deleterious effects by very high doses of corticosteroids promises to make the treatment of this life-threatening syndrome more rational.

Undersea Physiology

... New Insight into Decompression Sickness

Undersea exploration in search of new energy and food supplies depends on our ability to complete deep dives safely, yet in both men and animals bubbles form and appear in the tissues and blood stream following deep dives. Decompression sickness, or "bends," resulting from bubbles may be mild or severe if bubbles block blood flow to the lungs, heart, nervous system and bones. Recent advances in elucidating the process of bubble formation have been made. Investigations in animals show that diving activates the blood clotting process and clots may contribute to tissue damage. Previously bubbles were thought to form at surfaces where two liquids meet; now experiments indicate that it is the presence of solids in a liquid which initiates bubble formation and that microclots may serve to promote bubble formation. The question of when during the course of a dive these tiny clots form is under investigation. Using ultrasonic bubble detectors, it can be demonstrated that bubbles form when the gases being inhaled are switched, even when there is no change in

pressure during a dive. This new finding (isobaric bubble formation) has changed certain Navy submarine procedures. The ultrasonic bubble detector was also instrumental in demonstrating the presence of bubbles in symptom-free divers. Results such as these are being used to develop better prediction formulas for bubble formation so that decompression procedures can be improved.

Blood Substitutes

. . . Improved Fluorocarbon Compounds

A synthetic substitute for blood would be of great benefit as a supplement to transfusion in situations when blood is not readily available, as with mass casualties or in the emergency rooms of small hospitals. Blood substitutes may also prove useful for the perfusion and preservation of organs for purposes of transplantation. The introduction of substitutes capable of carrying oxygen but free of the cells and proteins contained in blood could open a new era in biomedical research and clinical medicine. Certain fluorocarbon compounds have the capacity to dissolve and transport oxygen with much the same efficiency as hemoglobin. They do not react with the tissues and are eliminated unchanged from the body. This biological inertness makes them highly promising. It has already been shown that animals whose blood has been completely replaced with a fluorocarbon solution can survive not only the procedure itself but the time required for the regeneration of their own blood.

The fluorocarbons most extensively studied up to now tend to form highly unstable emulsions. Current research efforts have focused on the development of new compounds with more nearly ideal properties. Several highly promising fluorocarbons, capable of forming stable emulsions, apparently nontoxic and rapidly eliminated, have already been identified. Although additional testing is required, these new compounds may well prove to be useful blood substitutes.

Hemophilia

. . . Improved Yield of Antihemophilic Factor (Factor VIII) from Plasma

The human clotting Factor VIII in the form of cryoprecipitate or dry concentrate is the mainstay of hemophilia therapy. Factor VIII is also widely used for experimental studies relating to a variety of clotting disorders other than hemophilia.

Plasma is the only source of Factor VIII. The usual methods for harvesting Factor VIII from this valuable material have been rather inefficient. Recently, a method has been developed by which the yield can be greatly increased. By the new technique, plasma that has been deep frozen in plastic packs as flat slabs is thawed in a water bath and allowed to siphon continually into an attached satellite pack external to the bath. This thaw-siphon procedure is completed within 55 to 65 minutes, and the cryoprecipitate, retained in the residual frozen plasma, contains 70 to 100 percent of the original plasma Factor VIII. Clinical observations in hemophilic patients treated with these cryoprecipitates have confirmed that the higher content of Factor VIII in plasma transfusions is associated with enhanced treatment effectiveness.

Hepatitis

. . . New Information on Methods To Control Post-Transfusion Infections

One of the most serious risks connected with blood transfusion is the transmission of hepatitis viruses from donor to recipient. While hepatitis B has been virtually eliminated as a transfusion hazard as the result of the introduction of highly sensitive tests, it has now become apparent that another form of the disease, "non-A, non-B hepatitis," remains a major hazard. A major advance in the field was the successful transmission of this form to chimpanzees, giving rise to the expectation that the virus (or viruses) responsible for this form will be definitely isolated and characterized, and that sensitive diagnostic tests can be developed. The epidemiology of non-A, non-B hepatitis is already under intensive study and has been found to resemble that of hepatitis B.

It has been demonstrated that freezing and washing of red cells from hepatitis B-infected blood donors cannot effectively remove the viruses and eliminate the risk of hepatitis in recipients. Therefore the search for methods that would protect those who must receive transfusions is being intensified.

Sickle Cell Disease

. . . Advance in the Development of Carbamylation Therapy

One treatment for sickle cell disease is the carbamylation of sickle hemoglobin by cyanate. The therapy is aimed at improving the survival of red

Chimpanzee colonies provide a valuable research resource for new studies on the characterization of non-A, non-B hepatitis, the most common cause of post-transfusion hepatitis.

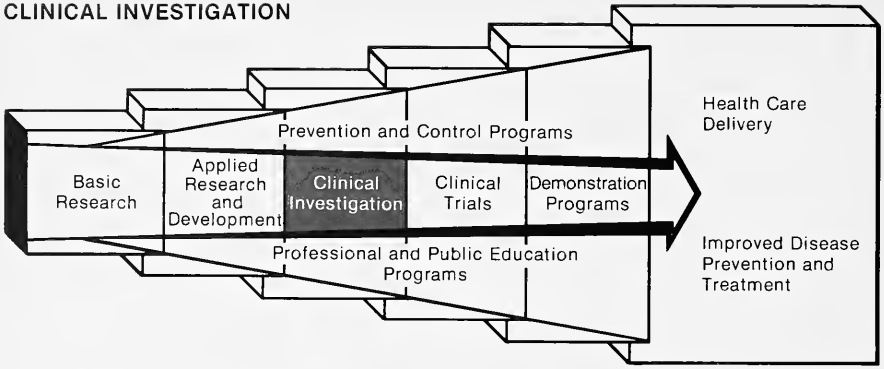
blood cells by decreasing the amount of sickling. Clinical trials have been undertaken and the results indicate that with therapeutic doses of oral cyanate painful episodes decrease in frequency and the severity and the degree of anemia improve. However, oral administration of cyanate results in serious side effects such as cataract formation and neurotoxicity. To obtain therapeutic levels of carbamylation without side effects, a program has been developed to expedite more efficient, rapid and safe techniques of carbamylating the cells outside the patient's body and then reinfusing the cells into the patient after free cyanate has been removed. The conditions for optimum carbamylation have been determined and achieved in experimental animals. A carbamylation apparatus for this procedure has been designed.

Thrombosis

... Progress in Detection

Blood clots which block circulation are a major cause of heart, lung, and cerebrovascular disorders. If blood clots can be diagnosed and located during early stages of development, they may be treated before circulation becomes severely impaired.

During the clotting process, fragments of various clotting factors are released into the blood stream and may then be detected by sensitive assays. Detection of increased concentrations of these chemical substances, through the use of sensitive assay techniques, may be an effective method for diagnosing intravascular clotting. Currently, various assay methods are being developed and tested for products of fibrinogen or fibrin hydrolysis by thrombin, prothrombin activation fragments, and platelet Factor IV, which are all indicators of clotting. A major advance in this area is the finding of a 0.88 correlation between levels of fibropeptide A, which is released during formation of a fibrin clot, and the presence of a thromboembolism. Such evidence reinforces the usefulness of these techniques in determining the onset of abnormal clotting. Recognition of abnormal intravascular clotting even before it is clinically manifested means that appropriate anticoagulant therapy can be initiated to reduce and even prevent subsequent thrombosis or embolism.



Clinical investigation is the vital link between basic and applied research and clinical practice. It provides the mechanisms for translating fundamental research results into potential clinical regimens. Clinical investigations, coupled with basic and applied research, are critical to developing effective therapies to alleviate or delay the effects and progression of disease as well as the design of preventive measures. Further, clinical research translates clinical observations into research focused on determining disease etiology.

Hypertension

. . . New Evidence on the Role of Dietary Salt

For many decades, low-salt or no-salt diets have been regularly prescribed for the majority of hypertensive patients whose disease has been characterized as essential or, more specifically, "of unknown origin." Since a measurable decrease in blood pressure has been recorded in large numbers of salt-restricted essential hypertensives, it has been assumed that all hypertensives have an inability to handle salt and that this inability is both a function of and an aggravation of their disease.

A recent clinical study suggests, however, that patients with essential hypertension can be divided into roughly equal salt-sensitive and non-salt-sensitive groups in which only the former need restrict their salt intake.

Studies suggest that only those hypertensive experimental animals that suppress their production of renin in response to a high salt load are able to excrete this high salt load promptly; those that don't suppress renin in this test increase their blood pressure further and are thus salt-sensitive. This observation suggests that the inability to handle salt is not caused by high blood pressure itself but, rather, is a concomitant of a failure to suppress renin. Interestingly, in humans there appears to be a racial difference between the abilities of normotensive black and white persons to handle salt. The black subjects do not excrete an administered salt load as efficiently as white subjects, and black subjects also show a greater suppression of plasma renin activity following the salt load. This may offer a clue to one possible reason for the substantially higher prevalence of hypertension in blacks than in whites.

Sudden Cardiac Death

. . . Advance in Means To Identify High-Risk Patients

About 60 percent of all cardiac deaths occur before the patient can be hospitalized, and the majority of these sudden deaths occur in persons who have a prior history of heart disease. Recent research has focused on means to decrease the rate of sudden cardiac deaths.

Earlier advances in this area are noteworthy. It was found that the proximate cause of death in most cases of sudden cardiac death is ventricular fibrillation (total incoordination of heart contraction). It was learned that such ventricular fibrillation and sudden cardiac death could occur without fresh heart muscle damage (acute myocardial infarction); it was noted that prompt resuscitation was effective in a significant fraction of such patients.

Prevention of sudden cardiac death rather than resuscitation of victims seems a more promising

large-scale solution. If a prophylactic, therapeutic regimen were to be found, persons at high risk would have to be identified.

It has long been recognized that the major risk factors for sudden cardiac death were basically the same as the risk factors for cardiac death, and, among these, the most powerful were the presence of previous heart attack and the extent and severity of myocardial damage thereafter. An additional important risk factor in survivors of myocardial infarction seems to be the severity of residual rhythm disturbances. Additional considerations such as heavy smoking, heavy alcohol intake, untreated diabetes, and hypertension are further risk factors.

Much work remains to be done to sharpen the specificity of the sudden death risk profile and particularly to extend it to those who are not yet recognized as having overt heart disease. Nevertheless, the knowledge that certain risk factors have been identified and are, to some extent, controllable opens exciting prospects that major inroads against sudden death can be achieved through early detection of high risk subjects. For example, clinical trial of chronic antiarrhythmic prophylaxis in survivors of heart attack has been undertaken.

Atherosclerosis

. . . New Information Concerning Normal Levels of Blood Pressure, Cholesterol, and Triglyceride in Young People

High blood pressure and high levels of cholesterol and triglyceride are all considered to be risk factors for atherosclerosis. However, to determine when a person's levels are sufficiently high to constitute a significant risk, one must first know what can be considered a normal level. Until recently, data were not available on normal cholesterol, triglyceride, and blood pressure levels for young people. This is especially important in light of the fact that a form of atherosclerosis has now been observed to begin during childhood. Recent findings have increased our knowledge of normal levels for young people.

The Lipid Research Clinics have recently made public data concerning cholesterol and triglyceride distributions derived from 16,000 subjects 0 to 19 years of age. Both clinic and overall analyses show that mean plasma cholesterol levels are lower in groups in their midteens than in preteen or late teen groups.

In a related development, the Specialized Centers of Research in Atherosclerosis (SCOR) have jointly published longitudinal data concerning the distribution of serum cholesterol and blood pressure in babies, children, and adolescents.

It is hoped that these data will assist in providing a basis for establishing normal values for blood pressure, cholesterol, and triglyceride levels. Using such values it would be possible to identify young people in whom these risk factors are significantly elevated. As one step in this direction the SCOR's are developing grid charts on which a physician can chart a child's blood pressure. It is hoped that these charts will be available for use in office practice in the spring of 1979.

Ischemic Heart Disease

. . . New Technique for Treating Coronary Obstructions Under Evaluation

Transluminal coronary angioplasty is a new technique which has been developed with the goal of relieving the obstruction of the more proximal coronary arteries without the need for coronary bypass surgery. In some ways, the procedure is similar to the diagnostic catheterization in which a fine tube is advanced from an arm or leg artery through the arterial system to the heart or into the coronary vesseis. With transluminal coronary angioplasty, a special catheter is used which has a tiny balloon at its tip. The tip of the catheter is advanced into the artery that is narrowed, and the balloon is momentarily distended at high pressure. This causes a forcible expansion and opening of the coronary narrowing. The balloon is deflated and the catheter withdrawn.

While this method offers promise, it is one with which there is little research experience. The technique is potentially applicable to patients with narrowings restricted to the proximal portion of certain coronary arteries and, thus, represent only a small fraction of patients now undergoing coronary bypass surgery. Investigators are now undertaking studies to determine the ultimate safety, efficacy, limitations, and side effects of applying this technique.

Atherosclerosis

. . . Drop in U.S. Plasma Cholesterol Levels

Despite the knowledge that high cholesterol levels are closely related to the development of atherosclerosis, our ability to control the amount of

cholesterol in the diet of a free population is quite limited. A wide variety of educational measures is presently being studied and recent evidence suggests that, at least in certain groups, education measures do affect eating habits.

Recent studies indicate that there has been a modest decrease in plasma cholesterol levels in the U.S. population at large concurrent with a decrease in the rate of cardiovascular deaths. Moreover, as compared to the rest of the population, slightly but significantly lower blood levels have been observed in men and women from higher education and occupational backgrounds. These findings are contrary to previous trends and suggest that the eating habits of these groups may have been affected by reports of the relationship between saturated fat intake, cholesterol levels, and coronary heart disease.

Ischemic Heart Disease

... Radioisotope Methods Developed To Detect the Size of Infarcts

The noninvasive technique of labeling red blood cells *in vivo* with technetium-99m pertechnetate has been used to obtain a stable radionuclide blood pool for several hours and to evaluate patients admitted to the hospital with chest pain. Serial measurements of ventricular ejection fraction and segmental wall motion have been used to more definitely establish the extent of myocardial injury and the frequency of in-hospital infarct extension in terms of assessing changes in regional and global contractility. The technique is used as a research tool for describing the course of acute myocardial ischemia and for assessing techniques to limit the size of infarctions; it is sometimes used for determining the extent of cardiac disease and identifying those at special risk or warranting special procedures.

Lung Defense Mechanisms

... Impairment by Cigarette Smoking

There is now substantial evidence that the lung uses a highly organized immune system in its defense against airborne substances. Recent evidence indicates that cigarette smoke may severely impair local immune defenses of the lung. Cells removed from the bronchoalveolar air spaces of otherwise healthy young smokers showed marked alterations in both cellular composition and physiological function. There was an increase in the proportion of alveolar macrophages, a decrease in the proportions of lymphocytes, and a significant increase in the proportion of T cells in these young, asymptomatic smokers. These results correspond with earlier findings reported from smokers with more clinically apparent lung disease. Thus, cigarette smoke may contain immunosuppressive factors and contribute to the increased incidence of respiratory infection in smokers, and this action may occur in the absence of other pathological symptoms.

Cystic Fibrosis

... Possible Mechanisms for Susceptibility to Chronic Lung Infections Identified

Cystic fibrosis is one of the major pediatric pulmonary diseases in the country, occurring in 1 out of 2,000 live Caucasian births. Children and young adults with cystic fibrosis are unusually susceptible to chronic lung infections from *Pseudomonas* bacteria; the reason for this unusual susceptibility has never been clear. These infections complicate the course of cystic fibrosis, are difficult to treat, and cause extensive lung damage. For the first time, investigators may be able to explain why patients with cystic fibrosis are so susceptible to *Pseudomonas* infections. Normally the white blood cells, or leukocytes, provide an important defense against bacteria. However, recent findings indicate that in patients with far advanced cystic fibrosis, the leukocytes are incapable of attacking even dead *Pseudomonas*. These same leukocytes respond quite normally to other types of bacteria and to several leukocyte stimulating agents (mitogens). Furthermore, another type of defense cell, the alveolar macrophage, is unable to ingest *Pseudomonas* bacteria after exposure to sera from cystic fibrosis patients. These findings are providing insight into this poorly understood disease and its secondary manifestation, and should be particularly helpful in designing more effective therapeutic approaches.

Sarcoidosis

... New Insights into Immunological Alterations

Sarcoidosis is a significant public health problem, especially among young blacks in whom it is 12 to 15 times more prevalent than in the white population of the United States. It is a multisystem disease of unknown etiology which almost always affects the lungs. Patients with this disease frequently have abnormalities of cell-mediated immunity which involve thymus-derived lymphocytes (T lymphocytes). A decrease in the number of T lymphocytes has been

noted in the blood of patients with advanced sarcoidosis who were not on steroid therapy. Sera from about half of a group of patients studied contained antibodies against normal T lymphocytes. It is unclear whether the antibody is the cause of the reduction of these lymphocytes or whether damaged lymphocytes result in the formation of the autoantibody. However, the antibodies to T cells identified in the sera of sarcoid patients may account for some of the immunologic abnormalities found in this disease. This advance in understanding sarcoidosis, a mysterious and often debilitating disease, may lead to improved diagnosis and treatment in the future.

Respiratory Distress Syndrome

... Biochemical Alterations in Surfactant

Surfactant lecithin from neonates with respiratory distress syndrome contains less palmitic acid than surfactant lecithin from infants without disease. It is thus of interest that recent studies on tracheal wash lecithins obtained from adult patients with evidence of post-traumatic adult respiratory distress syndrome (ARDS) suggest that a similar decrease in palmitic acid occurs in these patients. Abnormal lipids from the lungs of ARDS patients have also been noted to have altered physical properties. Thus, it appears that one consequence of severe trauma may be the production of abnormal surfactant, which could contribute to the pulmonary dysfunction in these patients. Although the role of surfactant in the adult syndrome is not yet understood, these findings suggest that the surfactant present in these adult patients may also have an abnormal chemical structure. These studies in human subjects are also evidence that the fatty acid composition of surfactant lecithin may be an important determinant of surfactant function.

Adult Respiratory Distress Syndrome

... An Epidemiologic Review

In spite of the advances in diagnosis, monitoring, and treatment of patients with adult respiratory distress syndrome (ARDS), no significant change in the mortality rate of these patients has been made in over 11 years. In 174 cases in one center, the average long-term survival was only 44 percent. In 10 large U.S. hospitals during 1977, the average survival rate for ARDS was only slightly better at 51 percent. Further data on 721 patients were provided from the nine centers participating in the Extracorporeal Membrane Oxygenator Clinical Trial to show that the overall survival rate was 32 percent. The potential for survival was significantly better for those ARDS patients with trauma and embolism than those with pneumonia or wet lung. However, all the studies clearly demonstrated the need for future work in the structural, biochemical, immunologic, and physiologic mechanism of acute lung injury and repair. A new SCOR program has been developed to address these research needs.

Berylliosis

... New Insights into Etiology and Treatment

Berylliosis, or beryllium poisoning, is a debilitating condition generally characterized by cellular masses primarily localized in the lung. Early detection and diagnosis has been a major problem in the management of this condition. Previously, diagnosis of this disease was based on symptoms and X-ray changes which occur only late in the disease. Recently, a laboratory test has been developed for diagnosis and clinical management. Using tissue culture techniques, white blood cells from individuals suffering from berylliosis showed a strong positive reaction when exposed to beryllium salts. Over 500 clinically healthy beryllium workers have now been screened by this method, and in 96 percent of the cases a completely negative result was obtained. The remaining 4 percent of the cases have shown a very weak reaction. These individuals are being carefully followed and retested several times a year. In related studies using a guinea pig model of berylliosis, it has been shown that the disease can be almost completely prevented by administering drugs which suppress the body's immunologic responses. This finding supports the theory that immune reactions are important in the development of the disease in man and suggests that the disease may be treated with currently available drugs.

Maturation of the Lung

... Mechanisms of Action of Epidermal Growth Factor

In the continuing search for factors that affect lung development, an epidermal growth factor that enhances fetal lung maturation in experimental animals has now been isolated from human urine and plasma. In animal models, epidermal growth factor has been shown to accelerate maturation of the pulmonary epithelium and to increase the number of type II (surfactant-producing) cells more than threefold. To bring these findings to bear on studies in man, a series of three radioimmunoassays for human epidermal growth factors has been developed, and is being used to study their excretion in

infants and adults. Daily excretion of this factor in the urine has been found to be low in newborn infants and young children, but, when calculated on the basis of body surface area, the levels are comparable with those in adults. This line of investigation is continuing to determine levels during pregnancy as well as in infants with and without respiratory distress syndrome, and to identify the tissue of origin of the growth factor and its role in human fetal development.

Thalassemia

... Steps Toward Improved Methods for Home Treatment

Frequent blood transfusions are a standard therapy for thalassemia. Because the thalassemia patient does not properly produce his own blood cells, the transfused cells must be replaced as they age and die. The transfused blood cells contain iron, and unfortunately, the transfusion therapy is accompanied by the serious complication of iron buildup which can destroy many of the body's organs. Much clinical research has focused on identifying the best types of transfusion therapies with the fewest deleterious side effects. Experiments have examined the best means to eliminate iron buildup. Desferrioxamine is a drug which can assist in extracting excess iron from the body and studies are examining the best ways to administer desferrioxamine as well as studying other iron-extracting drugs.

The results of recent studies confirm that long-term parenteral therapy with desferrioxamine, 20 milligrams per kilogram, administered subcutaneously, over an 8- to 12-hour period daily, constitutes adequate therapy for patients over 5 years of age. A portable pump permits home administration of desferrioxamine and by using this pump children can live essentially normal lives. Several new iron chelating agents are being studied. One of these, 2, 3-dihydroxybenzoic acid, has been found to be inefficient in humans but may be of value as an adjunct to desferrioxamine therapy. Rhodotorulic acid, however, appears to be more efficacious than desferrioxamine when administered intravenously. Chelyhydroxamic acid and ethylenediamine are under study in experimental animals.

Sickle Cell Disease

... Ophthalmologic Disorders

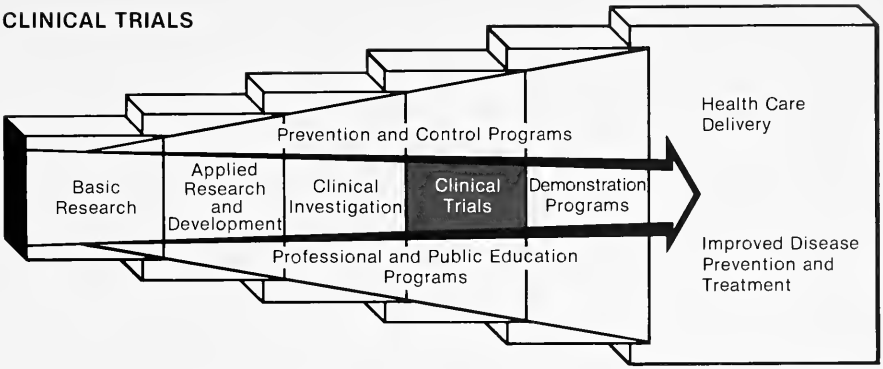
In addition to its devastating effects on red blood cells and related physiological mechanisms, sickle cell disease often produces severe ophthalmologic disturbances. These disorders of the visual system include neovascularization, aneurysms and retinal detachments. Through recent technological advances in photocoagulation, with xenon arc and argon lasers, the ophthalmologic consequences of sickle cell disease and other disorders of red blood cells have been documented. Presently, a collaborative study has been initiated to clarify and document the incidence and natural histroy of ocular conditions related to various hemoglobin types in the distinctive population and environmental conditions of Jamaica. Comparison and correlations will be made with findings from similar studies conducted in the United States. These data should increase the understanding of the wide spectrum of symptoms of sickle cell disease.

Hemophilia and Von Willebrand's Disease

... New Findings Related to the Treatment of Clotting Disorders

Hemophilia A and von Willebrand's disease are two inherited bleeding disorders. When severe, they can result in severe bleeding from even the most minor injuries. Recent research has defined the molecular defects in these two diseases, paving the way for testing new methods of diagnosis and treatment. Treatment usually involves transfusion of plasma fractions to replace the factor(s) necessary for clotting. One of these is Factor VIII, a coagulation-promoting protein in plasma. Both hemophilia A and von Willebrand's disease are associated with reduced levels of Factor VIII, but are quite different in other respects. Hemophilia A is carried by mothers who are symptom-free but transmit the disease to half of their male children. Von Willebrand's disease can be transmitted from either parent to children of either sex.

Platelets (blood cells that form clots) function normally in hemophilia; in von Willebrand's disease they do not. The researchers found that normal Factor VIII can correct the clotting deficiency in both hemophilia A and von Willebrand's disease. They also found that the synthesis of the Factor VIII protein in hemophilia is normal except for the deficiency of clot-promoting activity. The Factor VIII protein in von Willebrand's disease showed a spectrum of abnormalities. The most severe von Willebrand's cases show no Factor VIII protein in their plasma. In a less severely affected group, Factor VIII is present in reduced levels and the protein is abnormal. A third group of patients has Factor VIII protein normal in amount, structure, and clot-promoting activity, but is markedly deficient in ability to correct the abnormal platelet function of the disease.



Clinical trials test, in a carefully controlled setting, the efficacy and safety of preventive and therapeutic regimens with the potential to save hundreds of thousands of lives and billions of dollars each year. The clinical trial is a key step in the long, difficult, and complex process which converts research findings to clinically applicable prevention or treatment regimens.

The objective of the large-scale clinical trial — a critical activity in the biomedical research spectrum — is to gain information regarding the effect of a given form of medical or surgical intervention. Clinical trials are used to test new drugs, compare alternative patient management modes, determine the effectiveness of different treatments, or measure the efficacy of intervention programs for high-risk populations. Trial results validate the projection of potential consequences of successful intervention — risk reductions, changes in longevity, morbidity, and mortality, and economic savings.

The conduct of a clinical trial involves a series of steps, each with its own stringent requirements. Consequently, the time needed to successfully complete a trial can range anywhere from 2 to 10 years depending on the size and complexity of the trial. Successful completion of a trial involves the concerted effort of literally hundreds of scientists, clinicians, analysts, and support personnel; and the cost can reach tens of millions of dollars by the time a trial is completed and its results disseminated. Therefore, the decision to undertake a clinical trial is not made without considerable deliberation. Often, a small pilot trial is used to determine the feasibility of, and gains to be expected from, a larger trial.

The following examples of clinical trials emphasize the importance of this activity and the interrelationships among the various activities in the biomedical research spectrum.

Aspirin-Myocardial Infarction Study (AMIS)

... Secondary Prevention of Myocardial Infarction with the Drug Aspirin

It has been postulated that thrombosis plays a major role in the late stages of coronary artery occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. Theoretically, an agent which prevents the aggregation of platelets would be of value in people with coronary artery disease. Aspirin, in small doses, inhibits platelet aggregation for prolonged periods of time, and therefore might be expected to prevent or retard the occlusion of coronary arteries. This would be reflected in a decrease in the incidence of myocardial infarction and a decrease in mortality due to coronary artery disease.

Several studies have given preliminary evidence that regular administration of aspirin may be of benefit to patients with known coronary artery disease. A National Heart, Lung, and Blood Institute-sponsored study, the Coronary Drug Project, ran a pilot trial of aspirin and placebo in men with previous

myocardial infarctions. Preliminary results from this trial demonstrated its feasibility and led the NHLBI to sponsor a more definitive controlled study of the benefit of aspirin in the secondary prevention of coronary heart disease.

Patients have been recruited and randomized and are currently on therapy and under observation. Followup is for a minimum of 3 years with each patient seen at 4-month intervals and monitored for side effects and various nonfatal events, including cardiovascular problems. The primary endpoint is mortality. Annually, a detailed history is obtained and a complete physical examination performed. The study involves 30 clinical centers, a coordinating center, and central laboratory.

The study has completed patient recruitment in the scheduled 1-year period. Four thousand five hundred and twenty-four post-MI patients were enrolled by the 30 clinical centers. Three-year minimum patient followup will continue through summer 1979. Periodic reports on endpoints and toxicity are being reviewed by the Policy-Data Monitoring Board. There is evidence of good patient adherence to the study's drug regimen.

Management of Patent Ductus in Premature Infants

. . . Comparison of Treatment of Patent Ductus Arteriosus with Indomethacin and Conventional Medical Therapy

A clinical trial with two facets is planned to assess the relative merits of indomethacin and surgical intervention in infants with persistent respiratory distress who did not receive early indomethacin treatment.

The incidence of patent ductus arteriosus is higher in premature than in full-term infants and is highest in premature infants with respiratory distress syndrome. Some infants demonstrate signs of a large shunt during the course of respiratory distress syndrome. Many of these infants will improve with medical management of congestive heart failure, but others require surgical closure. A third group of infants with respiratory distress have severe progressive pulmonary disease requiring ventilatory support. There is disagreement concerning whether or not eliminating the patent ductus in these infants results in decreased mortality. A variety of therapeutic approaches are being used and there is no convincing evidence of the superiority of one treatment over another. This trial will test the efficacy of differing therapies under controlled conditions.

The study is currently in the planning stage which is expected to be completed early in 1979. Twelve clinical centers and a data coordinating center are participating.

Neonatal Respiratory Distress Syndrome

. . . Primary Prevention by Administering Corticosteroids

Neonatal respiratory distress syndrome is one of the leading causes of disability and death in the newborn. It is much more common in premature than in full-term neonates. In the United States, approximately 10 percent of all infants are premature, and each year about 50,000 cases of neonatal respiratory distress syndrome occur. Hospital costs average $5,000 per patient with an average stay of 23 days.

Extensive studies on animal models for respiratory distress syndromes have demonstrated that antenatal administration of synthetic and natural corticosteroids (dexamethasone and cortisol) accelerates lung maturation and significantly diminishes the occurrence of RDS. Only one large, controlled, double-blind clinical trial on antenatal corticosteroid therapy has been published to date, but this therapy is beginning to be widely used in the United States. In this trial, which was conducted in New Zealand, it is reported that there is a lower-than-expected incidence of neonatal RDS when beta-methasone is given to mothers for at least 24 hours after the onset of premature labor, and not later than the 32nd week of gestation. No followup data, however, have been published. Although a variety of conditions in newborn infants have been treated with steroids over the past 20 years without recognized adverse effects, investigations have been needed on the short-term effects of corticosteroids administered antenatally on neonate and mother, and on the long-term effects on the infant.

The planning phase of this trial was completed in March 1977, with formulation of a common protocol and manual of operations. Patient screening and enrollment began in August 1977 and is to last for 2 years. Followup will continue for 18 months after the entrance of the last patient. At the present time there are five clinical centers and a coordinating center in the trial.

Cardiovascular Health Education

. . . Testing the Outcomes of Mass-Media Campaigns and Counseling

To determine whether community health education can reduce the risk of cardiovascular disease, a field experiment has been conducted in three northern California towns. In two of these communities there were extensive mass-media campaigns over a 2-year period, and in one of these, face-to-face counseling was also provided for a small subset of high-risk people. The third community served as a control. People from each community were interviewed and examined before the campaigns began and 1 and 2 years afterwards to assess knowledge and behavior related to cardiovascular disease (e.g., diet and smoking) and also to measure physiological indicators of risk (e.g., blood pressure, relative weight, and plasma-cholesterol). In the control community the risk of cardiovascular disease increased over the 2 years but in the treatment communities there was a substantial and sustained decrease in risk. In the community in which there was some face-to-face counseling the initial improvement was greater and health education was more successful in reducing cigarette smoking, but at the end of the second year the decrease in risk was similar in both treatment communities. These results strongly suggest that mass-media educational campaigns directed at entire communities may be very effective in reducing the risk of cardiovascular disease.

Coronary Primary Prevention Trial

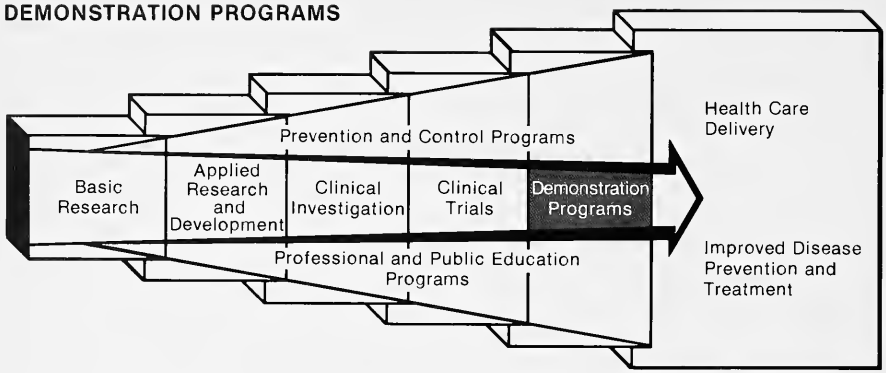
. . . Testing the Effects of Reducing Serum Cholesterol Levels

This trial, a double-blind study involving some 4,000 patients for 7 years is testing the hypothesis that long-term reduction of serum cholesterol in men with elevated cholesterol levels (but initially free of coronary heart disease) will lead to a lowered incidence of coronary heart disease. The study emanates from the Institute's Lipid Research Clinics, which carry out fundamental and applied research and epidemiologic studies of lipids and lipoproteins. Because arteriosclerosis is so intimately tied to clinical risk of coronary heart disease and because increased lipid levels are highly correlated with both arteriosclerosis and coronary heart disease, the study will provide significant data which could greatly facilitate the development of measures for preventing heart disease.

Hypertension Detection and Followup Program

. . . Evaluating the Effectiveness of Hypertension Control

While clinical research has demonstrated that appropriate therapy, in controlled clinical settings, can reduce morbidity and mortality in men with diastolic blood pressures above 105mm Hg, it is not known whether antihypertensive therapy, applied to hypertensives in the general population and making use of existing medical resources, can significantly reduce morbidity and mortality. The Institute therefore initiated a controlled, cooperative clinical trial, involving 14 clinics and 11,000 patients, to determine: (1) those significant operational, socioeconomic, motivational or behavioral factors which would influence the acceptance of antihypertensive therapy in a defined population; and (2) whether a practical intensive antihypertensive program can significantly reduce morbidity and mortality in a representative sample of hypertensives, in the general population or in selected population groups. The trial has significance as both a test of methods to effect hypertension reduction and a test of the effectiveness of such reductions in lowering morbidity and mortality.



Demonstration programs test methods to introduce or facilitate delivering health care advances to the public. Demonstration activities, which are a recent addition to the Institute's programs, have been implemented to effectively translate research findings into health practices. Such programs will be of even greater importance as more clinically applicable information becomes available for dissemination from ongoing clinical trials.

Smoking Prevention

. . . Testing the Peer Pressure Technique

Among the many methods for preventing or stopping tobacco smoking, none has been proven unequivocally effective. The many techniques have varying degrees of success, and it is very important to systematically identify known methods which have higher success rates.

One method which is currently under study is the peer pressure method for preventing young people from starting to smoke. It is hypothesized that young people respond strongly to social pressures from their leaders and their close companions, particularly in the schools. Methods for involving young people's companions in the effort to prevent smoking are now being tested in United States high schools.

The projects use behavioral techniques and train youngsters to cope with the pressures their peers would normally exert influencing them to smoke. They also train nonsmoking young people to discourage their friends from smoking, and even set up a peer leadership program to discourage adolescent smoking. While the final results of these efforts must be measured over a fairly long period of many individuals' maturation, preliminary results show considerable promise.

Nutrition

. . . Assessment of the Effects of Nutrition Education on Consumer Food Purchases

Assessing the kinds and quantities of foods that people eat is central to nutrition education efforts. NHLBI is now undertaking several innovative nutrition education programs designed to influence people's food choices at the points where they make food decisions such as at vending machines, cafeterias, and grocery stores. An evaluation has now been designed to test the impact of a year-long nutrition program in a major supermarket chain. The use of an inventory control cash register system in over 30 stores is expected to provide a direct, highly reliable record of the daily food selections of customers using these stores. As customers pay for their purchases, the cash register automatically records every food item selected. It is expected that the study will quantitatively describe the food selection habits of a large population for a period of years. These data will provide a sound empirical base line against which to evaluate trends in food selection patterns as well as the impact of the nutrition programs under study.

Nutrition

. . . Education in the Cafeteria

Several innovative approaches to changing food habits have been developed. Like successful food industry advertising practices, these approaches are designed to influence food habits at the moment when selections are made, whether at the supermarket, at work, or at home.

The "Food for Thought Game" is a nutritional education program designed for use in cafeterias. As customers go through a serving line, they pick up an attractively designed playing card that contains important nutritional information about available cafeteria foods. The messages encourage customers to consider such factors as calories and nutritional value when selecting foods. An evaluation of this program at one cafeteria indicates that this "game" effectively helped reduce average caloric intake during lunch. It appears that this program will now be disseminated nationally by the American Heart Association and the American Hospital Association.

Nutrition

. . . Changing Marketing Approaches

Vending machines represent a significant source of food sales in the United States. In cooperation with the National Automated Merchandizers Association (NAMA) and the Macke Company, NHLBI recently conducted a small campaign to evaluate the sale of nutritious yet lower-calorie vending machine items. Initial results indicate that, with the proper health marketing approach, lower-calorie nutritious foodstuffs can be a profitable sales venture. Expansion of this program concept is currently being discussed with the Macke Company and the NAMA.

Hypertension

. . . Educational Programs Begun in Worksettings

Cooperation with private organizations in business and industry is an important aspect of NHLBI's educational efforts. In the past year two new cooperative programs in hypertension control have been initiated.

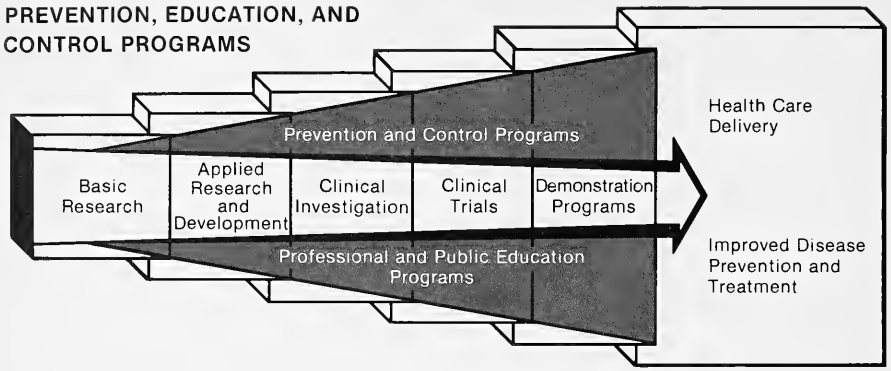
The University of Michigan and the Ford Motor Company are evaluating four different approaches to delivering high blood pressure control services in an industrial setting. Two additional contracts are being negotiated with other groups to evaluate other types of high blood pressure services in industrial settings.

Another demonstration worksetting effort is the Blue Cross Association education and training project. The aim of this program is to train Blue Cross account executives to provide their clients with consultation on planning and implementing high blood pressure control programs at the work site.

Hypertension

. . . Startup of Four High Blood Pressure Control Programs

Starting in 1978 the states of Connecticut, Maryland, South Carolina, and California have undertaken efforts to achieve statewide coordination of high blood pressure control activities. The outcomes will be evaluated through probability sample surveys of hypertension control status both before and after the program is implemented. Morbidity and mortality data will also be analyzed before and after initiating program activities to evaluate the health status outcomes of the program. It is anticipated that the program will be enlarged in the current fiscal year.



Clearly, the ultimate focus of the biomedical research spectrum—shown by the direction of the arrow in the diagram above—is improved prevention, education, and treatment of the cardiovascular, pulmonary, and blood diseases for which the Institute has responsibility.

Through the efforts of investigators at all levels of the research spectrum, several advances have emerged which offer great potential for the treatment and prevention of disease.

Atherosclerosis

. . . Available Data on Cholesterol and Fatty Acid Content of Common Foods and Fast Foods

Because of the close relationship between diet and atherosclerosis, prevention is expected to depend heavily on changing eating habits. For this reason, it is very important to determine the composition of common foods. At the present, the Nutrition Coding Center has completed its table for the following food constituents: calories, protein, total fat, total carbohydrate, alcohol, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated acids, sucrose, starch, other carbohydrates and fiber. The next priority for nutrients to be completed is linolenate: linoleic fatty acids, oleic fatty acid, and vitamins and minerals. This new information will be very useful in testing the effects of dietary manipulations and in developing preventive diets.

In addition, a large and growing proportion of the national diet is now provided by "fast foods"; yet, until recently, little information concerning the composition of these foods was available. NHLBI has recently received comprehensive fat-composition data from a sample of the most popular foods through an interagency agreement with the Department of Agriculture. For the first time, information has been provided on over 80 different fatty acids, taking into account their cis-trans configurations. These data provide valuable tools for studying the relationship between popular American diets and determinants of atherosclerosis.

Improving Medical Care in Community Hospitals

. . . Evaluation of Approaches

To upgrade medical care in this country, advances in prevention, diagnosis, and treatment must promptly be made available to health practitioners working outside of large research centers. Since 1974, the Institute has supported several educational programs designed to bring clinical advances to the community setting. In the past year, some of these projects were completed. They have resulted in the development of:

- Self-instructional programs on cardiopulmonary resuscitation for health care personnel and the public;
- A system for training emergency care teams from community hospitals at regional referral centers.

Followup evaluation demonstrated improved knowledge and some improvements in skills among

trainees. However, an audit of hospital charts was somewhat disappointing. No significant change in emergency care of adults with respiratory distress was evident by chart review criteria. A possible explanation of this lack of change in practice is that few patients with respiratory distress syndrome were seen by the trainees. This apparent lack of success in a pilot training program has helped point out the importance of having a needs assessment procedure to determine the educational needs of the trainees, a procedure which has been incorporated into some of the current programs supported by the Division. The effort to focus attention on the specific needs identified by the target audience is expected to increase the educational impact of the programs.

Therapeutic Plasmapheresis

. . . Techniques Used in Plasma Exchange

Plasmapheresis is a blood exchange procedure which permits the separate collection and removal of specific components of blood. The technique involves one or two plasma volume exchanges to effect the separation and often utilizes blood bank resources. The procedure removes certain components associated with disease and at the same time allows plasma to be obtained without wasting desirable components. Through the improved technology, plasmapheresis has now become a highly effective therapeutic approach for treating diseases such as myasthenia gravis, Factor VIII inhibitors, other immune disorders, and many genetic diseases, including the homozygous form of familial hypercholesterolemia (Type II hypercholesterolemia). As more is known about chemical irregularities of other diseases, plasmapheresis may become an important treatment for other conditions.

Atherosclerosis

. . . Lipid Research Clinics

Lipid Research Clinics have continued to act as a local resource for the diagnosis and management of hyperlipoproteinemia. Typical support includes assistance in standardizing local clinical chemical laboratories in lipid determinations, in providing consultation for individuals with special hyperlipidemic problems, in providing and disseminating heart-healthy nutritional information, and in making information on low-fat foods more available.

High Blood Pressure Education

. . . Increased Awareness and Expanded Efforts

There is evidence of substantial progress in controlling high blood pressure. Illness and premature death associated with high blood pressure are declining. This decline has accelerated during the past 5 years concurrent with a national program to control high blood pressure. The proliferation of vigorous high blood pressure detection and education activities has resulted in many people with hypertension beginning and maintaining treatment.

Recent surveys indicate that awareness of hypertension is markedly higher in areas where a high blood pressure education program has been conducted. One survey of 160,000 persons indicates that in an area served by a hypertension education program, only 29 percent of persons in the sample were unaware of their hypertension, while 6 years ago almost 50 percent of persons in a national probability sample were unaware of their hypertension.

In addition, there has been a 50 percent increase in patient visits for hypertension since 1972. It is estimated that there may be as many as 8 million Americans now on effective blood pressure control regimens. Concomitant with this increase in awareness there has been a decline in mortality for diseases associated with hypertension, notably coronary heart disease, stroke, and hypertensive disease.

These encouraging outcomes have led NHLBI to undertake a number of expanded programs in hypertension control. These include evaluations of the role of nutrition in hypertension control, the efficacy of high blood pressure control in the elderly, and the relative benefits and risks of treating mild hypertension. In addition to many other hypertension activities, NHLBI recently initiated a Black Health Care Providers Task Force to obtain a consensus on the role of black health care providers in detection, treatment, and management issues.

The BHCPTF has representatives from the Congressional Black Caucus, National Bar Association, National Black Nurses Association, National Dental Association, National Pharmaceutical Association, National Medical Association, Student National Dental Association, Student National Medical

Association, Student National Pharmaceutical Association, and National Heart, Lung, and Blood Institute. The group will prepare a position paper and develop an implementation plan to overcome identified barriers to effective cooperation.

Other minority support programs have included conferences, symposia, and seminars for the Asian-Pacific, Native American, and Spanish-speaking communities.

Blood Resources

... Newly Licensed Additive To Prolong Shelf Life

The Bureau of Biologics of the Food and Drug Administration (FDA) has recently approved the licensing of a product that will lengthen the shelf life of blood by 2 weeks. Research over the past 15 years has shown that by supplementing CPD* or ACD** with small amounts of adenine, the length of time that red cells remain sufficiently viable for transfusion is extended from 21 to 35 days. As a result of this research, the FDA announced in August 1978 that it was amending its regulations governing human blood and certain blood products to permit use of the anticoagulant citrate-phosphate-dextrose-adenine (CPDA-1). Correspondingly, the allowable storage period for whole blood and red cells was extended from 21 to 35 days when CPDA-1 is used as the anticoagulant.

The extension of shelf life made possible by the availability of adenine could have important consequences for the management of blood resources in the United States. Some experts believe that the greater flexibility allowed by a longer shelf life will mean reduced wastage due to outdating, less frequent shortages, and savings resulting from improved efficiency in collection and distribution.

*citrate-phosphate-dextrose
**anticoagulant-citrate-dextrose

V.
Status of Special Program Initiatives

SPECIALIZED CENTERS OF RESEARCH

Specialized Centers of Research (SCOR's) were begun in 1971 on the recommendation of the NHLBI Advisory Council and Congress. Initially the SCOR's addressed the areas of arteriosclerosis, hypertension, pulmonary diseases, and thrombosis; the area of ischemic heart disease was added in 1975. The SCOR's were established to meet the need for a planned, targeted, and coordinated national program of basic and clinical research specifically directed at improving the diagnosis, treatment, and prevention of particular diseases.

The diseases on which the various SCOR's focus inflict a tremendous burden in terms of sickness, death, and social and financial costs. Because of the size of this burden, the potential for making advances in prevention and control, and the magnitude of the scientific and clinical challenges, NHLBI has given high priority to developing SCOR's.

A SCOR is an identifiable organizational unit within its institution with a central theme to which individual projects relate. Each SCOR meets a rigid set of requirements that jointly distinguish the SCOR from regular project grants. Some characteristics of SCOR's are the following:

- The SCOR research program is goal-oriented, forming a planned attack on a specific disease or group of diseases.
- Each SCOR in a particular disease area participates in a continuous process of assessment and communication with related SCOR's, which greatly improves opportunities for coordinated studies and for dissemination of results.
- The SCOR must involve a cadre of established investigators in both the basic and clinical sciences, with an interest in the targeted disease area.

- SCOR clinical research staff must have access to facilities where sophisticated clinical investigations can be conducted, and to an adequate complement of patients suitable for study and long-term followup.
- A SCOR must include research laboratories and pathology, data management, biostatistical and other support necessary for the study of the targeted disease.

The SCOR program is now in its seventh year and its success has demonstrated the value of the mechanism in facilitating disease-oriented basic research, applied research, and scientific communications. The numerous SCOR accomplishments have been both institutional and substantive in nature. Some few of these accomplishments are summarized below.

Institutional Accomplishments

The SCOR program has helped bring about changes within and among the various participating institutions. These changes include:

- Improved interaction and collaboration among investigators within the host institution.
- Improved organization and participation in such matters as curriculum design, postdoctoral training, general education, and emphasis on preventive approaches.
- Broadened scope of interdisciplinary research through the attracting and better integrating of investigators from diverse but relevant disciplines.
- Better utilized and integrated joint core facilities.
- Increased collaboration and interdisciplinary projects among institutions.
- Broadened scope which has allowed scientific interchange at a national level.

Scientific Accomplishments

Hypertension SCOR's

NHLBI supports four SCOR's focused on the problem of hypertension. In the past year each of the SCOR's has conducted research projects with particularly interesting accomplishments. Some of these are summarized below:

- Several studies have converged to indicate that angiotensin vascular receptor behavior can be evaluated as a factor in hypertension and normotension. Studies have demonstrated that angiotensin blockade with either saralasin or teprotide can produce favorable blood pressure changes in patients with hypertension and congestive heart failure. A decrease in both systemic and pulmonary vascular resistance has been observed along with an increase in cardiac output. Left ventricular wall tension and myocardial oxygen consumption have also been reduced significantly.

  Other studies have demonstrated that changes in sodium balance per se can directly influence angiotensin vascular receptor behavior. Related studies have strongly suggested that the renin system actively participates in blood pressure maintenance of hypertensive patients. Up to 70 percent of all patients with common forms of essential hypertension exhibit this involvement. Studies further suggest that up to 30 percent of patients with essential hypertension can actually have their blood pressure normalized by saralasin angiotensin blockage. Further research based on these studies is now being undertaken.
- A behavioral study has made important observations concerning the relationship between community stresses and mortality from hypertensive diseases. A higher death rate from hypertension has been observed in divorced, separated, or widowed persons, and in economically deprived patients living in poverty or with substandard or overcrowded housing.
- Studies have characterized in detail the morphologic and biochemical changes occurring in the vasculature of rats with both genetic and experimentally induced forms of hypertension. Results indicate that hypertensive changes in the vessel wall can be made to regress with treatment of hypertension, but the changes do not necessarily fully return to normal. The longer the period of hypertension, the slower and less complete the regression.
- A recent study controverts the assumption that all hypertensive patients have an inability to handle salt. This study suggests that patients with essential hypertension can be about equally divided into salt-sensitive and non-salt-sensitive groups. Only those who have low renin levels appear to have special sensitivity to salt.
- Additional research on renin is beginning to elucidate the fundamental processes by which renin affects hypertension. A recent study indicates that

all of the renin in the kidney is of the high-molecular-weight form. There is also a circulating low-molecular-weight form of renin in spontaneously hypertensive rats. This exciting finding points to the possibility that the conversion of high-molecular-weight renin to the activated form may be a factor in the genesis of hypertension.

Arteriosclerosis SCOR's

NHLBI supports eight Arteriosclerosis SCOR's. Current activities in these centers include study of hyperlipidemia and vascular disease including animal and tissue studies and basic laboratory investigations. Some of the recent scientific accomplishments of the Arteriosclerosis SCOR's are summarized below.

- Studies of arterial metabolism suggest that low density lipoprotein (LDL) from hypercholesterolemic animals is more effective than high density lipoprotein (HDL) from normocholesterolemic animals in stimulating cholesterol accumulation and cholesterol esterification in arterial smooth muscle cells. These findings suggest a possible mechanism to explain the recently demonstrated inverse relationship of HDL and direct relationship of LDL with atherosclerosis progression in man.

- While it has been well established that obesity is an important factor associated with hypertension, epidemiologic studies suggest that obesity plays a lesser role in childhood hypertension. Statistical analysis reveals that obesity explains only a small part of the rise in blood pressure in children. For the most part, the relationship is with other maturational factors. A second important finding confirms the importance of a hereditary factor involved in hypercholesterolemia. Relatives of children with hypercholesterolemia have been observed to have a higher rate of mortality from myocardial infarction. This finding stresses the familial relationship between hypercholesterolemia and clinically apparent atherosclerosis.

- A wide range of basic studies has been undertaken on the interactions of various serum lipoproteins. Among the results are findings that HDL heterogeneity is associated with chemical differences in the protein moiety; and that HDL and LDL preparations can be modified *in vitro* to elicit variable responses in the proliferation of aortic smooth muscle cells in culture. Other lipoprotein studies indicate that phospholipids are equivalent in all classes of lipoproteins and that serum albumin plays an important role in stimulating phospholipase by decreasing Km (Michaelis-Menton Constant) for substrate.

- Several major contributions have been made to the knowledge of pediatric risk factors and the early natural histroy of arteriosclerosis, coronary artery disease, and hypertension. A concept of the onset of essential hypertension in early childhood has been proposed. In addition, a number of race and sex factors have been observed to influence risk factor variables. Other observations suggest the possibility of identifying individuals with multiple risk factors at a high level as early as age 5. Further study will be needed to determine the long-term predictability of these early manifest risk factors.

- Experiments with infant baboons suggest a strong hereditary factor in the determination of serum cholesterol levels. If these hereditary effects remain as the animals mature, the finding of such a strong genetic effect on serum cholesterol concentration early in life has important implications for detecting hypercholesterolemia in man.

- Studies are providing important new information about human platelets, the platelet-derived growth factor (PDGF), and some of the interrelationships between thrombosis and atherosclerosis. Platelet-derived growth factor is thought to play a critical role in promoting the internal smooth muscle cell proliferation associated with the development of atherosclerosis. Current research suggests that PDGF, platelet Factor IV, and B-thromboglobulin are released from platelets in parallel in response to stimulation by collagen or thrombin. Because the threshold for release of these substances is lower than for others, it is now thought that these substances are located in a separate group of granules in the platelet.

- Another accomplishment has been the demonstration that plasma fibrinopeptide A (FPA) levels are not elevated in patients with hyperlipidemia, as compared to normolipidemic individuals. No differences have been found in FPA levels in any of the different hyperlipidemic subgroups, or in the total hyperlipidemic group studied, compared to normals. Futhermore, no significant relationship has been found between FPA and serum lipid levels. These studies indicate that a steady-state increase in thrombin activity is not detectable in patients with uncomplicated hyperlipidemia. The studies suggest that abnormal (increased) intravascular coagulation is not present in patients

with hyperlipidemia. If there is an important association between hyperlipidemia, the initiation of atherosclerosis, and the hemostatic mechanism, this association is likely to involve platelets rather than coagulation factors.

- Studies on regional myocardial perfusion have produced several noteworthy accomplishments during the past year. In a series of experiments in dogs with partial coronary occlusion, measurements of regional myocardial blood flow performed using ^{133}xenon and a scintillation camera were found to agree closely with measurements of regional myocardial blood flow made with radioactive microspheres. These studies provide important validation for measurements made in patients with coronary arteriosclerosis who are studied at the time of cardiac catheterization. These data further demonstrated the potential usefulness of the radioactive xenon procedures for providing diagnostic information. In another study, the sensitivity and specificity of myocardial scintiscans performed after administration of only a single dose of ^{201}thallium in association with exercise stress testing (scans are made during exercise and 4 hours later) were explored. The effectiveness of this procedure in the noninvasive detection of myocardial ischemia and infarction due to coronary disease was found to be similar to that when ^{201}thallium is given on two occasions, during exercise and at rest several days later. The single-dose approach should make screening for coronary artery disease with ^{201}thallium scans less expensive and easier with less radiation exposure to the patient. These findings thus represent progress towards the objective of obtaining a noninvasive technique that is quantitative and that might be used to assess the degree of ischemic heart disease in individual patients and the effects of treatment programs in patients with hyperlipidemia.

Ischemic Heart Disease SCOR's

NHLBI supports nine Ischemic Heart Disease SCOR's. Current research in the Ischemic Heart Disease SCOR's addresses a wide range of biomedical issues including means of protecting ischemic myocardium, quantifying infarct size and testing methods of treating angina pectoris among others. A number of accomplishments have been made in the past year and some of these are summarized below.

- One of the important emphases of research in ischemia is aimed at developing and evaluating models and methods for measuring the effects of ischemia, studying myocardial and coronary vascular responses, and evaluating the effects of experimental therapy. Among other findings it has been demonstrated that alterations in regional myocardial shortening produced by aberrant electrical conduction are not a factor in producing contraction abnormalities during the early phases of myocardial ischemia; that propranolol produces favorable effects on regional myocardial function in some dogs during exercise in the presence of chronic coronary artery stenosis; and that pretreatment, in dogs, with propranolol and morphine reduces myocardial infarct size at 48 hours. Other findings include demonstration of safe support of depressed myocardium of myocardial injury or exacerbation of ventricular dysrhythmia; delineation of the specificity of the isoenzyme MB CK as a marker of myocardial injury in man; demonstration of improvement in regional perfusion in response to nifedipine and development and clinical implementation of the first radioimmunoassay for an isoenzyme.

- Clinical studies in patients with chronic ischemic heart disease and refractory ventricular dysrhythmias have demonstrated good efficacy of the new antiarrhythmic agent tocainide, particularly for suppression of ventricular tachycardia.

- During the past year, a study has been completed concerning the effects of morphine sulphate on left ventricular function and wall motion in patients with previous myocardial infarction. It had been proposed that morphine sulphate decreases preload and favorably affects myocardial oxygen demand. Findings indicate that morphine sulphate does favorably affect abnormal wall motion but does not alter preload in ventricular function.

- Studies of biochemical markers of ischemia have produced a very significant result in the past year. It has been demonstrated that the release of alanine is a sensitive indicator of the presence of ischemia.

- Important studies dealing with the mechanisms of myocardial injury following coronary bypass graft surgery have been completed. These studies show that, most commonly, transmural myocardial injury following coronary bypass graft surgery occurred in the distribution of successfully bypassed vessels. That is, at post mortem, examination of the graft was usually patent (78 percent). Histologic study of these areas demonstrated the presence of contracting band necrosis rather than

the more usual form of coagulation necrosis. Coagulation necrosis was seen in the remaining 22 percent of infarcts occurring in this setting. Since contraction band necrosis is seen in association with reflow ischemic insult and since contraction band necrosis is seen in the heart distal to patent grafts, it would appear that inadequate myocardial support procedures during the period of operative ischemia account for the majority of operative-related myocardial infarcts in association with coronary bypass graft surgery. This is contrary to the hypothesis that graft or intrinsic artery occlusions are the causes.

- Extensive pathologic studies of acute and healed myocardial infarcts have demonstrated that the majority of infarcts can be accounted for by coronary occlusion resulting from thrombosis arising on an ulcerated atherosclerotic plaque. Fifty-five patients have been studied in whom the etiology appeared to be related to coronary embolism as a result of valvular heart disease, cardiomyopathy, coronary disease or atrial fibrillation. Since coronary emboli tend to lodge distally and may recanalize, coronary embolism may be an important cause of myocardial infarction with angiographically normal coronary arteries.

- A number of studies have been completed which examined the effect of various vasodilators (particularly nitroglycerin) on regional myocardial blood flow to ischemic regions. In open chest animals without regional ischemia, administration of nitroglycerin has been shown to result in myocardial release of prostaglandin E associated with a decrease in coronary vascular resistance. This effect of nitroglycerin was partially blocked by the administration of indomethacin, an inhibitor of prostaglandin synthesis. Indomethacin can block completely the nitroglycerin-induced release of prostaglandin E. Thus, changes in myocardial blood flow induced by nitroglycerin may in part be related to its effect on prostaglandin E production. Other studies have provided further evidence that prostaglandins may have an important role in the regulation of collateral blood flow into areas beyond coronary artery occlusion. In these studies, indomethacin appeared to inhibit the magnitude of the time-related decrease in coronary vascular resistance after occlusion in the conscious dog.

Pulmonary SCOR's

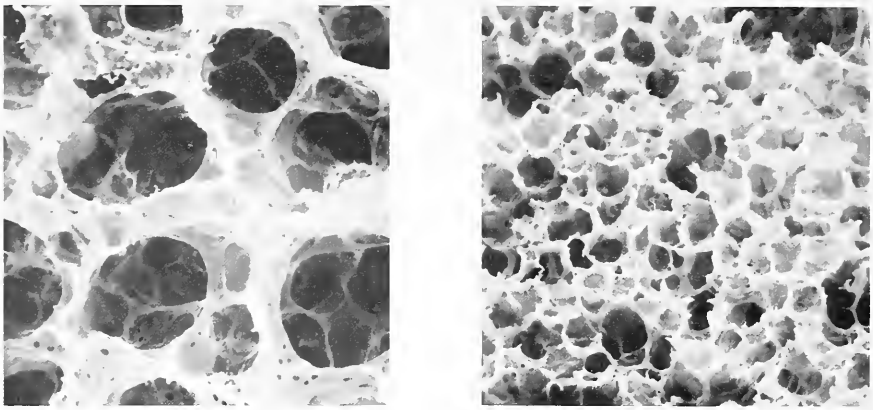
NHLBI supports 19 SCOR's concerned with the problem of pulmonary disease. In the past year these SCOR's have conducted a wide range of basic, applied, and clinical research projects. Some of the scientific accomplishments of these projects are described below.

- Fibrotic and Immunologic Disease SCOR's — Advances have been made regarding allergic bronchopulmonary aspergillosis which may allow improved diagnosis, evaluation and followup of patients with this disease. It has been observed that total serum immunoglobulin E (IgE) is elevated in cases of the disorder. IgE decreases during corticosteroid therapy in parallel with clinical improvement. IgE again becomes elevated during recurrences of the disease. Thus, IgE levels may serve as indicators of disease presence.

  Studies on both pulmonary lavage cells and fluids are extremely promising. Studies of the relative number of different lavage cell types, principally macrophages and lymphocytes, have shown that changes in differential cell counts parallel clinical disease activity. Differential cell counts are both predictive of the clinical disease condition of patients with pulmonary fibrosis, and they change in predictable fashion as a patient's disease process progresses or regresses. These lavage findings in patients with fibrotic lung disease show promise of investigative and diagnostic value.

- Cystic Fibrosis SCOR's — Lack of reliable bioassay procedures for factors or genetic markers unique to cystic fibrosis genotypes has thus far prevented a mass screening program for the disease. Recently, it has been shown that certain epithelial cells of the marine invertebrate *Spinunculus* produce mucus *in vitro* in response to a variety of stimuli including human body fluids. The extent of changes in the shape of these cells during mucus production appears to be a measure of the mucus-stimulating factor in the test fluid. If it can be demonstrated that these cells undergo predictable changes when exposed to body fluids from cystic fibrosis genotypes, this model could provide a test to identify persons at high risk for cystic fibrosis.

- Chronic Obstructive Lung Disease SCOR's — Cigarette smoking is considered to be the prominent risk factor for chronic obstructive lung disease and is the most important variable affecting symptom prevalence and lung function. In a long-term study in three centers, only 5 to 10 percent of asymptomatic nonsmokers studied gave abnormal results in a combination of pulmonary function



Scanning electron micrographs of lung from emphysematous mouse (tight-skin mouse with genetically transmitted disease) and from normal mouse. Note enlargement and deformity of alveoli in emphysematous lung on the left, compared to normal lung on the right (magnification 200x).

tests; on the other hand, in asymptomatic smokers, 33 to 38 percent of males and 30 to 56 percent of females showed abnormal results.

The earlier a respiratory problem can be diagnosed, the sooner it can be treated to prevent irreversible lung damage. Methods are being developed and reexamined as potential tools for early detection of respiratory problems. In the past, the chest radiograph has been useful in diagnosing obstructive disease only in patients with moderately or far advanced disease. However, a computer program to measure pulmonary volume from frontal and lateral radiographs has been developed which increases the information that can be obtained from the chest radiograph. A subtraction technique has also been developed which permits one to visualize structures containing small amounts of contrast substance while eliminating overlying densities which might obscure imaging of the structure of interest. This procedure permits a study of the evolution of the emphysematous lesion; visual determination of the site and nature of the airways obstruction in disease; and visual assessment of the effects of localized acute infection of the small airways. If the accuracy and effectiveness of this technique are validated, it will be a great aid in earlier detection and understanding of chronic obstructive lung disease.

- Pediatric Pulmonary Disease SCOR's — There is a greater incidence of respiratory distress syndrome in infants at the same gestational age delivered by cesarean section before labor than in those delivered by cesarean section after labor has commenced. Recent evidence suggests that oxytocin-induced labor increases both the initial rate of release of phospholipid into the alveoli and the total amount released in the first 24 hours after birth. In addition, it stimulates the activity of choline phosphotransferase, the enzyme which catalyzes the final step in the *de novo* synthesis of phosphatidylcholine. These findings suggest that labor stimulates both the synthesis and secretion of surfactant in the immediate postnatal period and thus may be an important factor in preventing the respiratory distress syndrome of the newborn.

Lung maturation and lung stability follow a developmental timetable. First evident in late fetal life, corticosteroids as well as other hormones have been implicated in this process. The mode of action of these hormones, however, is far from clear and is being investigated at the molecular level. In addition to glucocorticoid binding sites, it has now been shown that fetal lung cells and type II cells possess binding sites for thyroid hormones, suggesting that the lung is a potential target tissue for these hormones *in vivo*. Additional findings suggest that fetal, postnatal and adult rat lungs concentrate thyroid hormone from blood, and both thyroid hormone and adrenal corticoids may be necessary to induce accelerated lung development including enhanced maturation of type II cells.

Studies on human epidermal growth factor have resulted in the development of three radioimmunoassays that make observations of normal values for this hormone possible for the first time. The molecular size is the same as the mouse factor. Total daily excretion is low in infants and young children, although comparable to adult levels when expressed per body surface area. Moreover, there appears to be no difference in excretion between the sexes in preadolescent children and no significant daytime variation in excretion. Analyses continue during pregnancy and in infants with and without RDS to investigate the tissue of origin of human epidermal growth factor and its role in human fetal lung maturation.

Thrombosis SCOR's

NHLBI supports three SCOR's in the area of thrombosis. These SCOR's emphasize research in defining the pathogenic mechanisms of human thrombotic disease and methods for its diagnosis and treatment. In the past year a variety of scientific accomplishments have occurred, and some of these are described below.

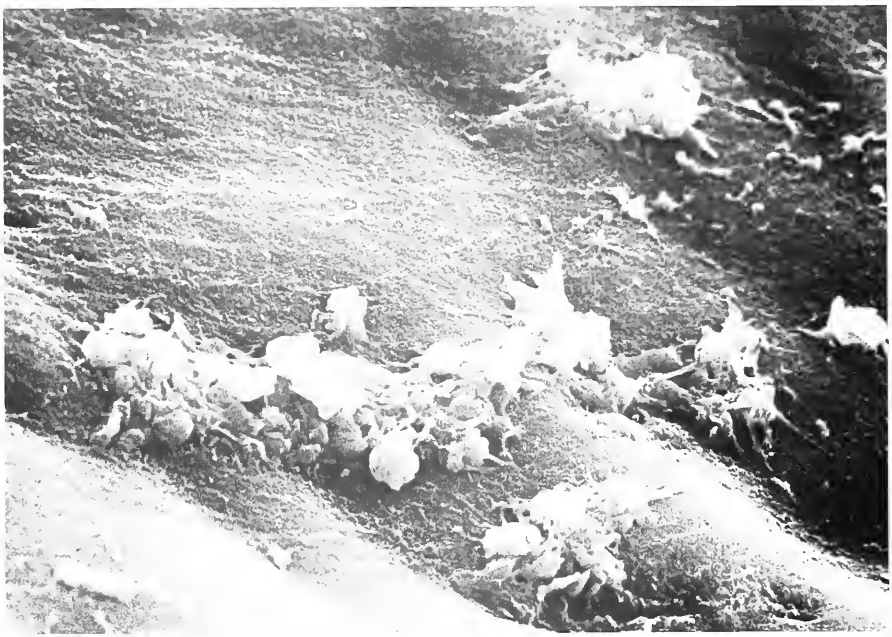
- One of the most interesting findings is that aspirin may have a beneficial effect in controlling thrombosis. The mechanism by which aspirin and other anti-inflammatory agents interfere with platelet function has been defined, and it has been demonstrated in human subjects that continuous daily doses of as little as 20mg will inactivate cyclooxygenase by 50 percent, suggesting that if aspirin has an antithrombotic action, it may be effective in very low doses.
- Progress has been made in developing techniques to visualize thrombi without invasive procedures. Studies are under way to test thrombus localizing agents with short half-lived high photon yield radionuclides and to test these *in vitro* and *in vivo*. In animal studies, ^{111}indium labelled platelets have been shown to be effective in the direct visualization of pulmonary emboli and deep venous thrombi less than 24 hours old. In the case of venous thrombi, it has been possible to image the damaged vessel wall rather than the thrombus itself.
- Recent studies of vascular injury in dogs are characterizing the way that arterial and venous walls change in response to injury. This research could have significant implications for understanding postoperative thrombosis. Results thus far indicate that the effects of surgical trauma on vessels remote from the site of trauma include altered endothelial surface characteristics and deposition of blood elements of endothelium products of tissue injury over a 4-hour period. This caused activation of the clotting mechanisms, venous damage, and blood cell accumulation. There was an absence of arterial damage.
- Studies of platelets and coagulation in patients with retinal vein occlusion have suggested that platelets may provide a trigger mechanism for venous thrombosis in the eye when local conditions permit. Preliminary studies suggest the possibility that variation in platelet coagulant activity concerned with early stages of intrinsic coagulation may determine whether patients with thrombocytosis will experience bleeding or thrombotic complications.

CLINICAL TRIALS

Clinical trials have become an important and, indeed, critical activity in the biomedical research spectrum. They constitute the essential final test of the effectiveness and safety of preventive and treatment regimens before they are introduced into practice. Clinical trials link clinical research with demonstration, education, and control activities by validating the effectiveness of therapies through controlled tests in human populations. In some cases, trials are used to determine which of several alternative treatments already in use is most effective. Thus, clinical trials have strong impact not only on the quality of health care, but on health care cost as well.

Clinical trials vary in scale from small studies involving only a few patients to long-term, complicated trials involving thousands of patients and many clinics across the country. Large-scale, controlled trials require the cooperation of investigators in many institutions nationwide, for no single institution has the necessary patient population or physical resources. To obtain comparable results, the participating institutions must adhere strictly to a detailed protocol, and because outcomes are often statistical measures of changes in morbidity and mortality of chronic diseases, these trials may require years to obtain definitive results.

Because of the extensive resources required by large-scale clinical trials, and the enormous potential impact on medical practice, the decision to initiate a trial must be careful and deliberate. The process of starting a trial begins with discussions among Institute staff, biomedical scientists, and health care researchers. Such discussions explore scientific and



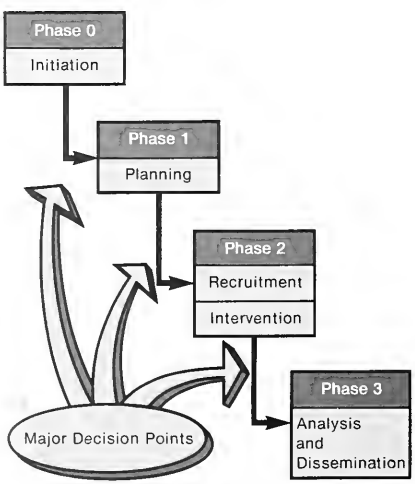
This electromicrograph pictures platelet aggregation on the blood vessel wall and is one of the imaging techniques used to study the process of clot formation.

health care developments which may have potential for improving the Nation's health. In most cases, the trial is the end of a long progression from basic science through clinical research and it is only after much study and planning that NHLBI devotes resources to a clinical trial.

Clinical trials are developed and implemented in a series of phases as represented in figure 6, The Clinical Trial Decision Process. The earliest phase (Phase 0) is the Initiation. During this phase, which takes place largely outside the Institute, the trial's concept is first advanced and skeletal trial designs are analyzed. The final trial designs and protocol are developed during Phase 1, the Planning phase. The design process involves investigators from *outside* the Institute as well as Institute staff. Following the planning phase, the protocol is analyzed again with respect to feasibility, the state of the science at that time, and the potential cost-effectiveness of the trial. After the review the Institute decides whether or not to commit resources to the trial itself. Phase 2, Recruitment and Intervention, represents the actual conduct of the trial beginning with recruitment of

Figure 6

The Clinical Trial Decision Process



subjects. This phase generally blends into the intervention phase during which the patients are treated and closely monitored. Throughout Phase 2, progress and data are analyzed by uninvolved experts both to ensure that the conduct of the trial is satisfactory and to monitor results which may dictate an early conclusion of the trial. Many analytic and ethical factors must be weighed, and the final decision for an early termination rests with the Institute Director. Following the recruitment and intervention phase, the trial enters Phase 3, the Analysis and Dissemination phase. In this phase, the trial results are analyzed and findings are disseminated to the medical and lay communities. During this phase, representatives of various aspects of the health care system, physicians, consumers, health planners, and third-party payers are brought together to develop consensus concerning the health care implications of the trial's results.

Table V lists each of NHLBI's ongoing clinical trials and indicates the current status of each. The following paragraphs briefly highlight the clinical trials presently sponsored by NHLBI and indicate the phase of each trial.

The primary prevention trials are testing means of preventing diseases before biological onset. Secondary prevention trials are testing interventions after the disease is detected which are designed to ameliorate the course of the disease, its mortality and morbidity.

Division of Heart and Vascular Diseases

The Division of Heart and Vascular Diseases has a number of trials now under way which are aimed at the primary prevention of coronary heart diseases. These clinical trials test the effects of reducing various risk factors. Cholesterol reduction is under test in the Lipid Research Clinic's Coronary Primary Prevention Trial (CPPT). It is also under test, along with cigarette smoking and hypertension, in the Multiple Risk Factor Intervention Trial (MRFIT) for the Prevention of Coronary Heart Diseases which is determining the effectiveness of reducing these risk factors simultaneously. Hypertension is under test in the Hypertension Detection and Followup Program (HDFP) which is examining the effectiveness of antihypertensive therapy on reducing morbidity and mortality in 14 communities. All of these trials have as their objective reducing morbidity and/or mortality related to coronary heart disease.

The Institute has several clinical trials related to secondary prevention and therapy for cardiovascular diseases. The Unstable Angina Pectoris Trial has been comparing the effects of medical versus surgical (coronary artery bypass graft) therapy on the survival and quality of life for patients with unstable angina. The Coronary Artery Surgery Study (CASS) is a major comparison of coronary artery surgery and medical management in patients with ischemic heart diseases. CASS patients are more typical of those currently undergoing coronary artery bypass surgery. Two other studies are concerned with drug therapy for the secondary treatment of cardiovascular diseases. The Aspirin Myocardial Infarction Study (AMIS) is examining the effect of aspirin on morbidity and mortality in postmyocardial infarction patients. The Beta-Blocker Heart Attack Trial (BHAT) is considering the effects of beta-blocker drugs in such patients. The mechanisms by which these two drugs act are significantly different. The beta-blocker drug acts on the electrical activity of the heart and the autonomic nervous system; aspirin affects blood platelets and arteriosclerosis development. The Multicenter Investigation of the Limitation of Infarct Size Trial (MILIS) is concerned with limiting the amount of heart muscle irreversibly damaged during myocardial infarction, and in this sense is a trial aimed at improving treatment of cardiovascular diseases.

Division of Lung Diseases

In the Division of Lung Diseases, a primary prevention trial of neonatal respiratory distress syndrome is aimed at newborns, particularly premature infants. The Extracorporeal Membrane Oxygenator Study, which was to determine the efficacy of this mode of treatment, has been completed, and the results are now being disseminated. Still other studies in the Division include a comparison of Intermittent Positive Pressure Breathing (IPPB) with the powered nebulizer, and the Nocturnal Oxygen Therapy Study, which compares that treatment to continous low-flow oxygen therapy in patients with chronic hypoxic lung disease.

Division of Blood Diseases and Resources

The Division of Blood Diseases and Resources is supporting the prevention and treatment-oriented Granulocyte Transfusion Study which is testing the prophylactic and therapeutic use of granulocytes to prevent or treat infections in patients with granulocytopenia. The Interruption of Maternal to Infant Transmission of Hepatitis B by Means of

Table V

Ongoing NHLBI Clinical Trials

Clinical Trial	Subjects	Status
	Division of Heart and Vascular Diseases	
Coronary Drug Project (CDP): Secondary prevention of coronary heart disease with drugs.	8,341 subjects followed for 5 to 8.5 years at 53 clinics.	Initiated in 1965. Recruitment and and Intervention completed in 1975. Now in Analysis and Dissemination, Phase 3.
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT): Primary prevention of coronary heart disease in hypercholesterolemic patients with the cholesterol lowering drug cholestyramine.	3,810 subjects followed for 7 years at 12 clinics.	Initiated in 1973. Now in Recruitment and Intervention, Phase 2.
Multiple Risk Factor Intervention Trial (MRFIT): Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pressure, and reducing or eliminating cigarette smoking.	12,866 subjects followed for 6 years at 20 clinics.	Initiated in 1972. Now in Recruitment and Intervention, Phase 2.
Hypertension Detection and Followup Program (HDFP): Evaluation of hypertension control to reduce total mortality.	10,940 subjects followed for 7 years at 14 clinics.	Initiated in 1971. Now in Recruitment and Intervention, Phase 2.
Unstable Angina Pectoris Trial: Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.	288 subjects followed for 9 years at 9 clinics.	Initiated in 1972. Recruitment and Intervention completed in 1976. Now in Analysis and Dissemination, Phase 3.
Coronary Artery Surgery Study (CASS): Treatment of coronary heart disease by coronary artery bypass surgery or medical management in patients with stable angina pectoris.	Over 700 subjects have been entered into this trial, which has a goal of 800 randomized patients, to be followed at least 4 years at 10 clinics. The study also includes a registry of over 23,500 patients with an eventual goal of 25,000 patients at 15 clinics.	Initiated in 1973. Now in Recruitment and Intervention, Phase 2.
Surgical Control of Hyperlipidemias: Prevention of myocardial infarction and death in survivors of myocardial infarction by partial ileal bypass surgery.	Approximately 180 subjects have been recruited into this trial, which has a goal of 1,000 subjects who are to be followed for 5 years at 3 clinics.	Initiated in 1973. Now in Recruitment and Intervention, Phase 2.
Aspirin Myocardial Infarction Study (AMIS): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug aspirin.	4,524 subjects to be followed for 3 years at 30 clinics.	Initiated in 1975. Now in Recruitment and Intervention, Phase 2.
Beta-Blocker Heart Attack Trial (BHAT): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug propranolol (a beta-blocker).	4,200 subjects are projected and will be followed for up to 4 years at 32 clinics.	Initiated in 1977. Now in Recruitment and Intervention, Phase 2.
Multicenter Investigation of Limitation of Infarct Size (MILIS): Treatment of myocardial infarction with the drug propranolol or hyaluronidase.	1,500 patients will be followed for 6 months in 5 clinics.	Initiated in 1977. Now in Recruitment and Intervention, Phase 2.
Treatment of Hypertension: Primary prevention of cardiovascular mortality and morbidity by drug treatment of hypertension with chlorothiazide plus *Rauwolfia serpentina*.	389 subjects followed for 7 to 9 years at 6 clinics.	Initiated in 1966. Recruitment and Intervention completed in 1976. Now in Analysis and Dissemination, Phase 3.

Table V

Ongoing NHLBI Clinical Trials (Continued)

Clinical Trial	Subjects	Status
	Division of Heart and Vascular Diseases	
Management of Patent Ductus in Premature Infants: Comparison of treatment of patent ductus arteriosis with the drug indomethacin, or with surgery, and conventional medical therapy.	540 subjects to be followed for 1 year at 12 clinics.	Initiated in 1978. Now in Recruitment and Intervention, Phase 2.
	Division of Lung Diseases	
Neonatal Respiratory Distress Syndrome: Primary prevention of neonatal respiratory distress syndrome by administering corticosteroids before birth.	800 subjects to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Recruitment and Intervention, Phase 2.
Intermittent Positive Pressure Breathing (IPPB): Treatment of chronic obstructive pulmonary disease with intermittent positive pressure breathing compared with powered nebulizer.	An estimated 1,000 subjects are to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Recruitment and Intervention, Phase 2.
Nocturnal Oxygen Therapy: Treatment of chronic hypoxic lung disease with nocturnal 12-hour oxygen therapy compared to continuous low-flow oxygen therapy.	300 subjects followed for up to 30 months in 6 clinics.	Initiated in 1966. Now in Recruitment and Intervention, Phase 2.
Extracorporeal Support for Respiratory Insufficiency (ECMO): Treatment of acute respiratory failure with an extracorporeal membrane oxygenator.	90 subjects were followed for at least 5 days in 9 clinics.	Initiated in 1974. Recruitment and Intervention completed in 1977. Now in Analysis and Dissemination, Phase 3.
	Division of Blood Diseases and Resources	
Granulocytes Transfusion Study: Primary prevention and treatment of infection in patients undergoing chemotherapy for leukemia.	An estimated 250 subjects to be followed for 3 years in 4 clinics.	Initiated in 1976. Now in Recruitment and Intervention, Phase 2.
Interruption of Maternal to Infant Transmission of Hepatitis B by means of Hepatitis B Immune Globulin: Prevention of hepatitis B in infants.	205 subjects to be followed for 3 years in 1 clinic.	Initiated in 1975. Recruitment and Intervention completed in 1978. Now in Analysis and Dissemination, Phase 3.
Cooperative Study of Factor VIII Inhibitors: Factor IX treatment of persons with hemophilia A and inhibitors to Factor VIII.	70 subjects followed for varying lengths of time in 11 clinics.	Initiated in 1978. Now in Recruitment and Intervention, Phase 2.
	Division of Intramural Research	
NHLBI Type II Coronary Intervention Study: Evaluation of lowering cholesterol with the drug cholestyramine in Type II hyperlipidemics in coronary artery disease regression.	143 subjects followed for 5 years at 1 clinic.	Initiated in 1971. Now in Recruitment and Intervention, Phase 2.
Diffuse Fibrotic Lung Disease: Treatment of idiopathic pulmonary fibrosis by azathioprine versus prednisone.	30 subjects followed for 1 to 3 years in 1 clinic.	Initiated in 1974. Recruitment and Intervention completed in 1978. Now in Analysis and Dissemination, Phase 3.
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis: Treatment of iron-overload with the agent desferrioxamine.	50 to 65 eligible subjects followed for 3 years in 2 clinics.	Initiated in 1973. Now in Recruitment and Intervention, Phase 2.

Hepatitis B Immune Globulin Study is a prevention trial in which babies of mothers with a high level of hepatitis B antigen are treated with hepatitis B immune globulin within 72 hours of delivery. The Cooperative Study of Factor VIII Inhibitors, a therapeutic trial, seeks to evaluate the therapeutic value of prothrombin complex concentrates (Factor IX) in patients with hemophilia A who have inhibitors to Factor VIII.

Division of Intramural Research

The Division of Intramural Research is supporting three clinical trials. The NHLBI Type II Coronary Intervention Study is assessing the effect of lowering cholesterol in patients with hypercholesterolemia and angiographically demonstrated coronary disease. It is using angiography to measure regression, thus providing a quantitative endpoint on the regression of atherosclerosis. The Diffuse Fibrotic Lung Disease Study is determining the relative effect of azathioprine and cortisone therapy on interstitial lung diseases. In the Trial on the Evaluation of Chronic Chelation Therapy for the Treatment of Transfusional Hemosiderosis, thalassemia patients are being treated for iron overload with desferrioxamine.

RESEARCH AND DEMONSTRATION CENTERS

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423), as amended by the Health Research and Health Services Amendments of 1976 (P.L. 94-278), authorizes the Director of the Institute to provide 30 new National Research and Demonstration Centers (NRDC) devoted to an accelerated attack on heart, blood vessel, lung, and blood problems. The Act provides for continued "basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention and treatment methods," for "ten new centers" in each of the areas of heart and vascular diseases, lung diseases, and blood diseases and resources. Only three such centers have been implemented at this time due to fiscal constraints.

The NRDC program was developed to apply the results of scientific research to health care and disease prevention by integrating research with education, training, and community demonstrations. Attached to major medical complexes and working closely with the NHLBI, the NRDC's hasten the transfer of new medical knowledge and technology to medical practice. The outstanding feature of the NRDC program is its utilization of education, training, and demonstration activities in close coordination with basic and clinical research. This type of continuous integration allows dissemination of the latest advances in medical research and treatment techniques.

Although only 4 years have elapsed since the funding of these centers, it is clear that the NRDC concept is a useful one. This success is due largely to the unique atmosphere in the centers, provided by the diverse and highly skilled health science professionals. Of utmost importance is the interaction among specialized scientists and practitioners. Their coordinated efforts and expertise expedite evaluation and implementation of improved treatment techniques. Specific accomplishments in the NRDC's cover a broad range of activities, from laboratory research through clinical demonstration to education of the health researcher, provider and consumer. NRDC's aid NHLBI in particular aspects of the National Program Plan and establish valuable knowledge networks among academic institutions, voluntary organizations, community hospitals, practitioners, and state health departments in their regions. The following sections summarize some of the activities and accomplishments of the NRDC programs during the past year.

National Research and Demonstration Center (Heart and Vascular Diseases)

The National Research and Demonstration Center program in cardiovascular diseases is mainly concerned with heart and blood vessel diseases, particularly arteriosclerosis and related studies of smoking, nutrition, and hypertension. Some of the ongoing and planned activities in the research component of this Center include the following:

- The Center has developed a laboratory concerned with lipoprotein structure and function. This laboratory has brought multiple physical-chemical techniques to bear on apoprotein structure and lipid binding properties. The laboratory has recently analyzed the complete amino acid sequence of human apoprotein C-1 of VLDL (very low density lipid), has synthesized it, and has shown that the synthetic protein has essentially the same properties as the natural apoprotein.
- Arising from this basic research interest in lipoproteins, the Center has developed a community program directed at demonstrating and evaluating the effect of certain dietary changes on the blood lipids of normal volunteers from the community. The diet program has demonstrated that serum cholesterol can be lowered in this group. The Center is now

Synthetic components allow much improved surgical treatment for heart and blood vessel defects.

The role of patient/physician communication in adherence to hypertension regimens is currently being evaluated in the Institute's Heart and Vascular Diseases National Research and Demonstration Center.

studying the extent to which dietary instruction needs to be carried out to achieve such a decrease in serum cholesterol.

- Other research projects planned or ongoing at the Center include the physiology of heart muscle; the causes, effects, and therapy of coronary-artery and heart muscle disease; and the surgical management of heart and blood vessel disease.

Some of the ongoing and planned education and demonstration activities in the Cardiovascular Research and Demonstration Centers include:

- Social-physiological projects to thwart smoking in school children including:
  - A field intervention program using behavioral techniques to discourage smoking due to social and peer pressure.
  - A program to train children to identify and cope with social pressures which influence them to smoke.
  - A study of children's attitudes towards smoking after being taught about the consequences of tobacco smoke inhalation.
  - An antismoking intervention project in four junior high schools based on peer pressure, physiological monitoring and the influence of antismoking commitment groups.
  - A peer leadership program to discourage smoking in young adolescents.
  - A field study of children's reaction to "fear-appeal" nonsmoking advertising.
- Nutritional programs including:
  - Community group demonstrations to lower blood lipids through dietary education.
  - A program to evaluate alternative approaches to promoting dietary changes in the general public.
- Hypertension programs including:
  - Continued use of standardized methods for screening, diagnosing and treating hypertension in community health centers.
  - Efforts to improve communication between patients and providers concerning the patient's hypertensive condition and its treatment.

National Research and Demonstration Center (Pulmonary Diseases)

The National Research and Demonstration Center for pulmonary diseases works to improve understanding, prevention, and management of respiratory disorders. Specifically the Center is concerned with primary and secondary prevention as well as rehabilitation of the disabled person. Planned and ongoing programs in the education and demonstration component of the Center include:

- The Center has developed a computer-assisted preoperative evaluation (CAPE) system to aid in the preoperative identification of patients likely to have respiratory problems during and following surgery. Computer-assisted interpretation of pulmonary function tests assists the surgical team in minimizing the patient's risk of respiratory distress.
- Investigators at the Center have reported finding in the lungs of smokers a high concentration of a substance which is found on tobacco leaves. This substance could be a causative agent in the pulmonary complications of smoking, or serve as a carrier of harmful substances in tobacco smoke into the smallest recesses of the lung.
- The Center is conducting a program to encourage physicians in the State of Vermont to use blood gas values as a diagnostic and monitoring tool. A computer-based "interpretation system" allows physicians in Vermont to call in blood gas measurements of their patients and receive rapid interpretation of the data.

Some of the planned and ongoing programs in the education and demonstration component of the Pulmonary Research and Demonstration Centers include:

- Development of a health professional education program for home health nurses and physical therapists who provide services and information to persons with chronic respiratory problems.
- Design and implementation of a health care program responsive to the needs of persons with chronic respiratory disease.
- Development of a lung cancer and cigarette-smoking intervention program to scientifically demonstrate and evaluate strategies for changing the smoking behavior of identified population groups.
- Development and use of an on-site computer-assisted teaching system to facilitate training in solving problems related to the quality of care and treatment for respiratory diseases.
- Establishment of group patient education programs to help patients with chronic obstructive pulmonary disease to understand their illness, receive physical therapy, and develop self-help and coping techniques.

National Research and Demonstration Center (Blood Resources)

The National Research and Demonstration Center in Seattle concentrates on acquiring, analyzing, and processing blood and blood products, in a continuous effort to improve blood services and resource management as well as clinical techniques and patient care.

Planned or ongoing programs in the research component of the Center include:

- A major component of the Center's responsibility to the community is the maintenance of the highest level of quality in the products and services that the Blood Center provides. Much of the effort has been in the direction of formulating a system of continuously monitoring the quality of products and services delivered by the Center. This program emphasizes periodic evaluation of the proficiency and quality of the work of laboratory personnel both in the central crossmatch lab and in the satellite laboratories; the development of a system for insuring the quality of reagents used in laboratory work; the development of an education system for both the initial training of laboratory personnel and remedial training when necessary; development of a system of mutual assistance between cooperating laboratories for maintaining a consistently high quality of work.

Planned or ongoing activities in the education and demonstration component of the Blood Resources Research Demonstration Center include:

- A progressive regional blood donor program to fulfill community needs for blood resources.
- Improvement of a data processing system for managing blood donor services.
- Provision of medical facilities and services including an outpatient transfusion service, hemophilia care program, and several specialized blood consultation services.

- Continuing education for laboratory trainees, public and professional education, and multidisciplinary care in the area of hemophilia management.

PREVENTION, EDUCATION, AND CONTROL

The ultimate goal of all NHLBI programs is improvement in the prevention and control of heart, lung, and blood diseases. Such improvements are, of course, founded in basic and clinical research. Considerable knowledge has been acquired in recent years concerning many of the diseases under the NHLBI mandate. However, biomedical research results cannot improve the quality of life unless research findings are widely communicated and applied. NHLBI's program of prevention, education, and control is aimed at speeding the transfer of knowledge into the mainstream of clinical medicine and personal health practices.

A major effort to provide the professional and lay public with education and information is under way. Implicit in this effort is the recognition that information and education can have a marked impact on the everyday health practices of Americans. Thus, programs are targeted at a broad audience including the general and lay public, medical and scientific communities, members of organized groups such as voluntary agencies, professional educators, representatives of the press and the media as well as Congress and state and local governments. The understanding that successful educational efforts must bring about observable behavioral changes is a key component of the program. Related to this philosophy, one of OPEC's major emphases has been evaluation of health education and information programs, in addition to program planning and implementation.

The following section summarizes some of the activities and accomplishments of prevention, education, and control programs during the past year. In addition to these programs, the National Research and Demonstration Centers all have major prevention, control, and education programs. These are discussed in the descriptions of Research and Demonstration Centers presented earlier in this section.

High Blood Pressure Education Program (HBPEP)

There is evidence of substantial progress in controlling high blood pressure. Premature death and illness associated with high blood pressure are declining. This decline has accelerated during the past 5 years concurrent with a national program to control high blood pressure. The proliferation of vigorous high blood pressure detection and education activities has resulted in many hypertensives beginning and maintaining treatment. However, large numbers of hypertensives are aware of their condition but are on either inadequate treatment or no treatment at all. These aware but uncontrolled hypertensives represent the greatest challenge to the National High Blood Pressure Education Program.

Indicators reflecting the Program's impact were reviewed during FY 1978 and they are generally quite favorable. Two of three screening surveys indicate that there is markedly greater awareness and control in areas of greater hypertension control activity. Some indicators of Program impact since the 1971 base-line year include:

- A 50 percent increase in patient visits to physicians for high blood pressure, as compared to a 5 to 6 percent increase in visits for all other causes.
- An increase in hypertension control programs from a few hundred to several thousand.
- Survey indications that a substantial majority of physicians generally follow the NHBPEP stepped-care treatment guidelines.
- Sharp decline in death rates for diseases most associated with hypertension (stroke, hypertensive heart disease, and coronary heart disease).
- Striking improvement in the level and quality of statewide hypertension control programs.

It is gratifying to witness these changes concomitant with the development of the High Blood Pressure Education Program.

Among the activities which the Program feels have made significant contributions to this success are:

- Technical assistance to state and community organizations.
- Assessment of public and professional educational materials.
- Cooperative public education involving local and national organizations.
- Programs of professional education.

- Cooperation and enhanced communication with voluntary health agencies.
- Demonstration programs involving industry, major health insurance carriers, State High Blood Pressure Coordinating Programs, and others.
- Scientific publications.
- National conferences and special purpose seminars and symposia.
- A wide range of special studies, task forces, and projects.

National Heart Nutrition Education Program (NHNEP)

The NHNEP goal is to promote healthy nutritional practices among the American population. Relationships between dietary habits and many cardiovascular risk factors are well established. For example, in many cases sodium, fat, and excessive body weight exert a demonstrable effect on blood pressure, blood lipid levels, and glucose tolerance respectively. More precise causal links between specific dietary factors, such as saturated fats and sodium, and major cardiovascular diseases, such as atherosclerosis and hypertension, are currently under study. While these validation studies continue, the Institute is committed to finding out how to help our citizens help themselves to alter dietary habits and seek health-maintaining behavior.

A consumer receives heart nutrition information through a new NHLBI program which is testing the effectiveness of educational approaches in a major supermarket chain.

Achieving this goal has required a collaborative approach actively involving NHLBI and influential organizations such as the food industry, media, education, and voluntary organizations as well as other branches of the Federal government such as the Food and Drug Administration and the Department of Agriculture. Among the recent accomplishments of this cooperative effort are:

- Development of public information and education methods about food and nutrition which impact at the time of selection in the supermarket, at work, or at home. Activities in this area have included advertising pilot projects in cafeterias, changes in the kinds of items available in vending machines, and information campaigns in a major supermarket chain.
- Development of a plan for targeting nutrition information to hypertensive persons in cafeterias, restaurants, supermarkets, and homes.
- Pilot studies of dietary change programs involving intensive intervention efforts for persons with hyperlipoproteinemia. Initial results indicate that intensive intervention measures, while having high initial success, lose effect over time if not continued and do not produce permanent dietary changes.
- Evaluation of special counseling programs (employing behavioral modification principles) for persons who fail to adhere to prescribed dietary protocols.

Clinical Trials Translation

The multicenter clinical trial, the vehicle for validating practical uses of research advance, has become a critical component of Institute programming. Several of the Institute's program elements are actively engaged in translating the results of clinical trials into medical practice. The mission of these efforts is to assure timely dissemination of NHLBI research results to targeted audiences. Thus, effective communication of clinical trial results to practicing health care professionals and the public is clearly an important component of Institute policy. As one participant in this undertaking, prevention, education, and control programs are presently involved in a number of projects for clinical trials translation.

VI. Program Goals and Planned Activities, 1979-1983

Program goals and planned research activities are developed by the scientific staff of the NHLBI with extensive additional advice from NHLBI advisory committees and task forces and with input from other leading biomedical scientists and review prior to implementation by the National Heart, Lung, and Blood Advisory Council.

The general program goals for 1979-1983 in heart and blood vessel diseases identify current areas of research priority and effort. The specific research activities listed for 1979-1983 are examples of research but are not intended to be inclusive. New opportunities are continuously emerging. These become evaluated for their potential significance and, if promising, become incorporated according to priority within the further research plans.

HEART AND BLOOD VESSEL DISEASES

Arteriosclerosis

Program Goals: 1979-1983

The Institute's mission is to improve the diagnosis, treatment, cure and prevention of arteriosclerosis and arteriosclerotic disease beyond that which is possible at present. The following goals have been developed to serve as guidelines for research activities during the next 5 years:

- Gain a better understanding of the pathogenic mechanisms in arteriosclerosis.
- Further specify associated or causal disturbances and associated risk factors for arteriosclerosis.
- Define those circumstances that may promote the regression and/or prevention of arteriosclerosis.
- Develop information on behaviors that promote or inhibit the application of knowledge about arteriosclerosis to its prevention, diagnosis, and/or treatment.

Research Activities: 1979-1983

The chief priority of the Institute's research activities continues to be the achievement of a better understanding of atherogenesis and the application of this information to more effective diagnosis, treatment, and prevention of arteriosclerosis. It has become increasingly clear that while we can predict susceptibility to arteriosclerosis by analysis of an individual's risk factors, many cases of disease remain unexplained and additional causal and risk factor data must be found. To this end, the Institute will continue basic and applied research and initiate a number of new studies.

Continuing research efforts include:

- Studies on the cellular mechanisms of atherogenesis.
- Increased involvement of investigators from the fields of blood coagulation, blood platelet research, and thrombosis to elucidate the effects of platelets and normal and abnormal plasma constituents on atherogenesis.
- Pathogenetic studies including those designed to elucidate the nature and significance of arteriosclerosis or its risk factor antecedents in childhood.
- Further development of our understanding of the roles of diet and nutrition in atherosclerosis and its control.
- Development and implementation of bioassays to test the effect of smoking on cardiovascular disease and determination of why smoking promotes atherosclerosis.
- Research on diabetes mellitus as a risk factor for, and important participant in, many aspects and mechanisms of cardiovascular disease.
- Multigenerational, longitudinal, and epidemiological studies in Framingham and other cohorts.

Studies to be implemented:

- Research on the genetics of hyperlipidemia and other risk factors and their potential role in coronary heart disease prevention.
- Research on the possible monoclonal origin of arteriosclerosis and on the role of intimal smooth muscle cells and platelets in atherogenesis.
- Utilization of the nonhuman primate resources developed for research in arteriosclerosis, cerebrovascular disease, and hypertension.

Studies under consideration of increased support:

- Research on the identification and study of additional "risk factors," with the objective of elucidating additional causes of premature coronary heart disease and other atherosclerotic complications. This effort will include basic, clinical, and epidemiologic research and will encourage studies of animal models, infants, and children. Special attention will be given to identifying risk factor antecedents of arteriosclerosis in childhood.

Hypertension

Program Goals: 1979-1983

Better understanding of the physiological systems that control blood pressure and the means by which these systems can initiate and/or exacerbate the developmental process of hypertension could result in a significant reduction in the incidence of hypertension as well as in more effective therapy among those already afflicted. The following basic goals have been established by the Institute as guidelines for research during the next 5 years:

- Emphasize research on etiology and pathogenesis of hypertension.
- Encourage development of improved methods and techniques for all aspects of hypertension research.
- Identify important new areas for research emphasis through the Hypertension Task Force activities.
- Broaden the interdisciplinary base for contributions to hypertension research by attracting scientists to this field who traditionally have not been involved or those unaware of the magnitude of their potential contributions if their efforts were directed toward this area of research.
- Complete the Hypertension Detection and Followup Program (HDFP).
- Implement effective models of high blood pressure control on a community-wide basis.

Research Activities: 1979-1983

Over the next 5 years, a steady progress toward realizing the Institute's mission is anticipated as a result of the following research activities.

Continuing research efforts include:

- Clarification of the role of renin as an initiating factor in essential hypertension; the role of

mineralocorticoids in hypertension; the role of urinary kallikrein in the pathogenesis of hypertension; and the relation of renal prostaglandin metabolism to hypertension.

- Research on inhibitors of renin and angiotension.
- Continuation of the Hypertension Specialized Centers of Research Program.
- Further studies on the epidemiology, etiology, pathogenesis, diagnosis, treatment, and prevention of hypertension in the young.

Studies to be implemented:

- Research on the efficacy of the treatment of high blood pressure in the elderly and on the role of nutrition in the management of hypertension (salt and weight control).
- Research programs on central neural control of blood pressure and the effects of hypertension and vasoactive agents on the vasculature. New emphasis will be placed on studies of how the brain participates in hypertension and in blood pressure control.
- Research on inhibitors of kallikrein, bradykinin, and various prostaglandins.
- New research initiatives as recommended by the report of the Hypertension Task Force due to be completed in FY 1979.

Studies under consideration for increased support:

- Etiologic studies including research projects to develop chemical antagonists to several physiological hormones which may be involved in the development of high blood pressure.
- Possible expansion of the Hypertension Specialized Centers of Research Program after FY 1980.

Cerebrovascular Disease

Program Goals: 1979-1983

The mission of the NHLBI in the area of cerebrovascular disease is to elicit further information on the pathogenesis of cerebrovascular disease and to enhance programs that will accomplish this goal. Thus, the major goals of the program are to:

- Gain further basic understanding of the pathogenesis of cerebrovascular disease.
- Encourage increased research activity exploiting the recent development of animal models of cerebrovascular disease.
- Develop noninvasive instrumentation to facilitate the diagnosis and observation of disorders of the large vessels supplying the brain.

Research Activities: 1979-1983

In the next 5 years it is hoped to increase substantially the research activity supported by the Institute in this area. The research opportunities afforded by the recent development of animal models of cerebrovascular disease will also be exploited. Specifically, the program plans are as follows:

Continuing research efforts:

- Basic etiologic and pathogenic studies relevant to cerebrovascular disease.
- Epidemiologic studies to identify environmental factors and personal characteristics which predispose persons to increased risk of stroke and to vascular chronic brain injury. Such studies are being conducted in the Framingham Study, the Lipid Research Clinics, the Multiple Risk Factor Intervention Trial, and the Hypertension Detection and Followup Program. Progress of these studies will be carefully monitored.
- Information, demonstration, and education programs aimed at influencing Americans to reduce or eliminate those factors — such as uncontrolled hypertension, high cholesterol levels, and cigarette smoking — known to be associated with the development of cerebrovascular disease. This is a goal of the Multiple Risk Factor Intervention Trial now in progress.

Studies to be implemented:

- Expand the program by notifying the research community that cerebrovascular disease is an area of special Institute interest.
- Initiate a program of short-term small grants to encourage preliminary or exploratory research, of an interdisciplinary nature, on the pathogenesis and complications of cerebrovascular disease.
- Request applications to study lesion pathogenesis in particular animal models.

In this "open heart" procedure, surgeons repair a heart defect with a patch of synthetic material. Great strides have been made in the reduction of postoperative mortality through research funded by the NHLBI

Coronary Heart Disease

Program Goals: 1979-1983

The ultimate objective directing the Institute's choice of program goals for the next 5 years is to further decrease mortality from coronary heart disease. Since it is not possible to quantify the effective contribution of a specific research program to the saving of lives and productivity, as well as the savings in hospital and rehabilitation costs resulting from the decreased death rate from 1970 to 1977, an unequivocal basis for the assignment of program priorities cannot be established. Accordingly, the essential thrust of already established programs will be continued together with ongoing assessment procedures. In addition, flexibility to pursue promising initiatives not yet identified will be maintained.

The specific goals through which the Institute plans to further reduce death and disability from coronary heart disease are the following:

- Improve the recognition and assessment of latent coronary artery disease and overt coronary heart disease.
- Improve the therapy of patients with acute myocardial infarction and patients with chronic ischemic heart disease.
- Assess the proper role of coronary artery bypass surgery in the management of ischemic heart disease.
- Assess possible methods for the reduction of the incidence of sudden cardiac death.*
- Develop techniques for reducing the amount of heart muscle irreversibly damaged during the course of myocardial infarction.**
- Develop methods of reducing the incidence of recurrent myocardial infarction.
- Improve rehabilitation of patients with coronary heart disease.

Research Activities: 1979-1983

To achieve these program goals, the NHLBI will support research efforts including the following:

- Specialized Centers of Research on Ischemic Heart Disease will broaden their emphasis to include aspects of coronary heart disease beyond the current major emphasis on acute myocardial infarction. Greater focus will be concentrated on chronic angina pectoris, rehabilitation, and early recognition of patients with coronary artery disease still in the presymptomatic stage.
- Expansion of research emphasizing the recognition of presymptomatic coronary artery disease as a means of identifying those at risk of developing acute and potentially lethal episodes of heart attack and sudden cardiac death. Importance will be placed on techniques such as the combination of radioisotopic assessment of ischemic zones during exercise and a variety of other methods.
- Evaluation and dissemination of the results of the clinical trial in the recently completed studies on unstable angina pectoris to improve the assessment of indications for, and long-term effects of, coronary bypass surgery.
- Expanison of studies in the area of sudden cardiac death including recognition of high-risk groups, improved understanding of what converts chronic coronary artery disease into an acute ischemic episode including death, and the means of prophylaxis.
- Completion of studies designed to reduce the recurrent rate of myocardial infarction and updating of the assessment of the chronic use of aspirin as a prophylaxis against recurrence.
- Promotion of community surveillance programs to track trends in coronary heart disease morbidity and to document changes in risk factors and prevention practices.
- Investigations of environmental factors, such as weather, trace metals, and degree of water hardness which might affect coronary heart disease morbidity and mortality.
- A trial of chronic prophylactic antiarrhythmic therapy in patients at heightened risk for sudden cardiac death, i.e., survivors of an acute myocardial infarction.

Peripheral Vascular Diseases

Program Goals: 1979-1983

The Institute's broad goal in the area of peripheral vascular disease for the next 5 years is to improve techniques for the diagnosis and treatment of peripheral arterial and venous diseases.

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* See section on arrhythmias.

** See section on heart failure and shock.

Specific goals over the next 5-year period are to:

- Develop more effective noninvasive methods of evaluating the severity of peripheral arterial diseases, suitable for the assessment of symptomatic patients, for the recognition of latent arterial diseases, and for research assessment of new modes of therapy designed to retard or reverse atherogenesis.
- Improve the management of patients with peripheral arterial diseases, with particular attention to the long-term effects of arterial grafts and the improvement of graft techniques for smaller arterial vessels.
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.

Research Activities: 1979-1983

To achieve these goals, the Institute plans to pursue the following research initiatives during the period 1979-1983.

Continuing research efforts include:

- Further development of noninvasive techniques for detecting and quantifying atherosclerosis in the clinical setting.

Studies under consideration for increased support include:

- Improvement in techniques for the grafting of smaller caliber peripheral arteries, including the development of synthetic graft materials.
- Evaluation of the long-term reliability of prosthetic graft materials now in use.
- A greater research effort in peripheral venous disease, for example, varicose veins.

Arrhythmias

Program Goals: 1979-1983

As is so often the case in man's search for new knowledge, solution of a problem usually generates more questions than answers. When knowledge of the variety and characteristics of arrhythmias was vague, research focused principally on collecting and classifying descriptive information. Now that sophisticated monitoring systems routinely provide these data, the focus of NHLBI research is on improving the understanding of, and the means to prevent, lethal arrhythmias. Consequently, the broad goals of the Institute now are to define the fundamental processes of electrical rhythm and conduction disorders and to develop methods of acute and chronic preventive therapy.

Specific goals of the Institute over the next 5 years are the following:

- Develop an improved understanding of the mechanisms whereby arrhythmias arise.
- Develop methods of chronic prophylactic therapy, using pharmacological agents, to prevent sudden cardiac death.
- Assess the role of pacemakers in the management of various conduction disturbances and define the indications for their use.
- Achieve a better understanding of the significance of rhythm disturbances commonly found in long-term, ambulatory monitoring of electrocardiographic rhythm to permit better clinical management.
- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Research Activities: 1979-1983

To achieve these goals the Institute plans to pursue the following research areas during the next 5 years:

- Studies of sudden cardiac death, with particular attention to identifying those at heightened risk and to characterize the fundamental mechanisms which convert chronic coronary artery disease into an acute process.
- Elucidation of fundamental mechanisms of rhythm disturbances.
- Studies to determine the significance of various rhythm and conduction disturbances in the general population and their correlation with risk.
- Clarification of the significance of various conduction disturbances and evaluation of the role of pacemakers in such circumstances.
- Improvement in automated methods for reading long-term (24-hour) rhythm monitoring tapes for the assessment of risk and therapeutic efficacy in ambulatory individuals.
- Development and distribution of standard reference rhythm monitoring tapes showing a variety of dysrhythmias to permit the comparative assessment of automated devices for reading heart rhythm tapes.

- Assessment of the possible therapeutic efficacy of chronic antiarrhythmic therapy with beta-adrenergic blocking agents.

Heart Failure and Shock

Program Goals: 1979-1983

In the next 5 years the Institute plans to further define mechanisms, improve diagnostic techniques, and develop methods for the prevention and treatment of heart failure and shock of cardiogenic origin. Specific Institute goals are to:

- Elucidate the fundamental, biochemical, and cellular mechanisms involved in myocardial ischemia and gain a better understanding of the systemic effects of cardiogenic shock.
- Develop methods for protecting ischemic myocardium and for preventing the conversion of reversible ischemic tissue to irreversible infarcted and scarred myocardium.
- Develop methods for quantifying the extent of ischemic myocardium to aid the assessment of therapeutic efficacy and patient management.

Research Activities: 1979-1983

Research activities for the next 5 years will focus upon the fundamental biochemical derangements associated with myocardial ischemia. As this research progresses and new knowledge is developed and validated, the NHLBI program in this area will focus increasingly on bringing potential therapeutic interventions to fruition and on decreasing morbidity and mortality.

- Investigation of the biochemical and cellular mechanisms involved in myocardial ischemia.
- Elucidation of the systemic effects of cardiogenic shock.
- Development of methods for the protection of myocardial ischemia and for preventing the development of irreversibly infarcted and scarred myocardium.
- Development of clinically applicable methods for quantifying the extent of myocardial ischemia.

Studies to be implemented include:

- A collaborative clinical trial on protecting ischemic myocardium will assess the ability of several pharmacologic interventions to reduce the amount of myocardial ischemia which develops into irreversibly scarred tissue during the process of acute myocardial infarction.
- Assessments of the applicability, precision, and limitations of several promising techniques for determining the extent of myocardial ischemia in postinfarction patients.

Congenital and Rheumatic Heart Diseases

Program Goals: 1979-1983

The economic value of prevention of congenital heart defects and rheumatic heart diseases versus their cure is one of the best examples of cost-effectiveness in medical care today. Knowledge of this fact and the need to provide still better means to diagnose and treat those already afflicted are the concepts underlying the Institute's research program during the next 5 years.

During that period, the Institute's research program will be directed toward achieving the following three goals:

- To better understand the etiology of congenital heart defects.
- To improve surgical techniques for repair of defects and noninvasive techniques for diagnosis and treatment of patients with congenital heart defects.
- To educate the public and practicing physicians in the diagnosis and treatment of throat infections, particularly those of streptococcal origin.

Research Activities: 1979-1983

Over the next 5 years, the Institute's continuing research efforts will include programs designed to:

- Develop improved techiques for the recognition of congenital and rheumatic heart diseases.
- Develop improved methods for preventing the occurrence and recurrence of rheumatic heart diseases.
- Facilitate the long-term followup of patients who have received the benefit of surgical repair for specific congenital heart defects.
- Determine the efficacy of pharmacologic agents for the management of certain forms of congenital heart diseases.

Cardiomyopathies and Infections of the Heart

Program Goals: 1979-1983

The goals of this program area over the next 5 years are:

- To further clarify the causes of cardiomyopathies.
- To develop more effective methods for diagnosis and treatment.

Research Activities: 1979-1983

To achieve these goals, the following research activities are planned.

Continued research efforts:

- Develop techniques for the recognition and management of cardiomyopathies and assess their prognostic significance.
- Elucidate the causative factors and mechanisms in cardiomyopathies.
- Develop improved methods for the recognition, treatment, and future assessment of myocarditis of various forms.

Circulatory Assistance

Program Goals: 1979-1983

Depending on the extent to which cardiac function is compromised, circulatory-assist devices may be required to relieve, in varying degrees, the work load of the heart or to perform the entire pumping function in place of the heart. The kinds of devices suitable depend not only on the degree of cardiac function which must be restored but also on the timespan during which such lifesaving support is required. Thus, the broad goal of the Institute in this program area is to develop and test, in priority order, short-, intermediate-, and long-term circulatory-assist devices for clinical use.

Specific goals include:

- Develop and test, for circulatory-assist systems, components such as pumps, engines, and control systems.
- Develop and test biocompatible materials suitable for circulatory-assist and other cardiovascular device applications.
- Develop and extensively bench and animal test circulatory-assist devices, particulary of the left ventricular assist type.
- Conduct clinical trials for assessing the efficacy of, and defining the clinical indications for, left ventricular assist devices.
- Support the research and development of other circulatory-assist devices.

Research Activities: 1979-1983

Targeted efforts will focus on the development and testing of implantable system components and systems suitable for intermediate- and, ultimately, long-term use. Specifically, the following research activities will be supported during the next 5 years.

Continuing research efforts include:

- Development of pumps which lend themselves to mechanical and hydraulic actuation since intermediate- and long-term implantation devices require other than pneumatic actuation.
- Development of electrically energized engines rather than radioisotope-energized engines, and of methods of transmitting electrical energy into the body by percutaneous leads or electromagnetic transmission.
- Assessment of materials showing promise for adequate blood compatibility and appropriate mechanical properties for long-term implantation requirements.
- Studies of the fundamental characteristics that define blood compatibility of materials.
- Validation of the long-term reliability of devices for clinical investigative use through detailed bench testing and extensive animal studies.
- Clinical studies of short-term devices.

Studies under consideration for implementation:

- Clinical studies with completely new devices suitable for intermediate- and long-term use (many months to years).

LUNG DISEASES

Structure and Function of the Lung

Program Goals: 1979-1983

The overall goals for the Institute in this sphere are to increase understanding of the normal structure, biochemistry, immunology, cell biology, and physiology of the developing and adult respiratory system, and to determine how these are altered prior to clinical onset and during the course of pulmonary disease.

The specific goals by which this mission will be accomplished are as follows:

- Determine the structural and functional characteristics of, and the interrelationships among, various types of lung cells, their modification in diseases, and their response to injury.
- Characterize the structural components — collagen, elastin, proteoglycans, and basement membrane — of the normal lung and the changes associated with specific lung diseases.
- Characterize the endocrine, immunologic, and other nonrespiratory functions of the lung and their modification in disease.
- Determine the physiologic factors controlling ventilation and transport of gases, and how adjustments are made to increase oxygen needed during normal stress situations (such as exercise and high altitude) and in pulmonary disease.
- Use physiologic principles to develop techniques for assessment of pulmonary function in infants, children, and adults.

Research Activities: 1979-1983

Since 1972, when the orientation of the Institute's program concerned with lung structure and function became inquiry at the cellular and biochemical rather than the organ physiological level, tremendous advances have been made. Research detailed below will carry forward this progress toward the ultimate goal of decreasing mortality and morbidity due to pulmonary disease.

Continuing research efforts include:

- Development of methods to separate major lung cell types into homogeneous and variable populations and to determine the ultrastructural and biochemical characteristics of individual lung cells.
- Studies of the mechanisms of lung tissue damage and repair.
- Investigations of the role of proteoglycans in lung function and growth, and their modification in emphysema and pulmonary fibrosis.
- Studies of intermediary metabolism of lung, using perfused lung, lung slices, and isolated lung cells.
- Studies of basic lung physiology, the role of chemical, mechanical, and neural mechanisms in the control of ventilation, and the processes of gas exchange in the immature and mature lung in health and disease.
- Development and evaluation of noninvasive techniques to measure pulmonary function in infants, children, and adults.

Studies under consideration for increased support:

- Investigations of the chemical structure, molecular architecture, and biosynthesis of connective tissue components in normal lung, evaluation of differences occurring with age, environmental influences, and specific lung diseases.
- Role of pulmonary membranes in the transport of gases, water, and solutes.

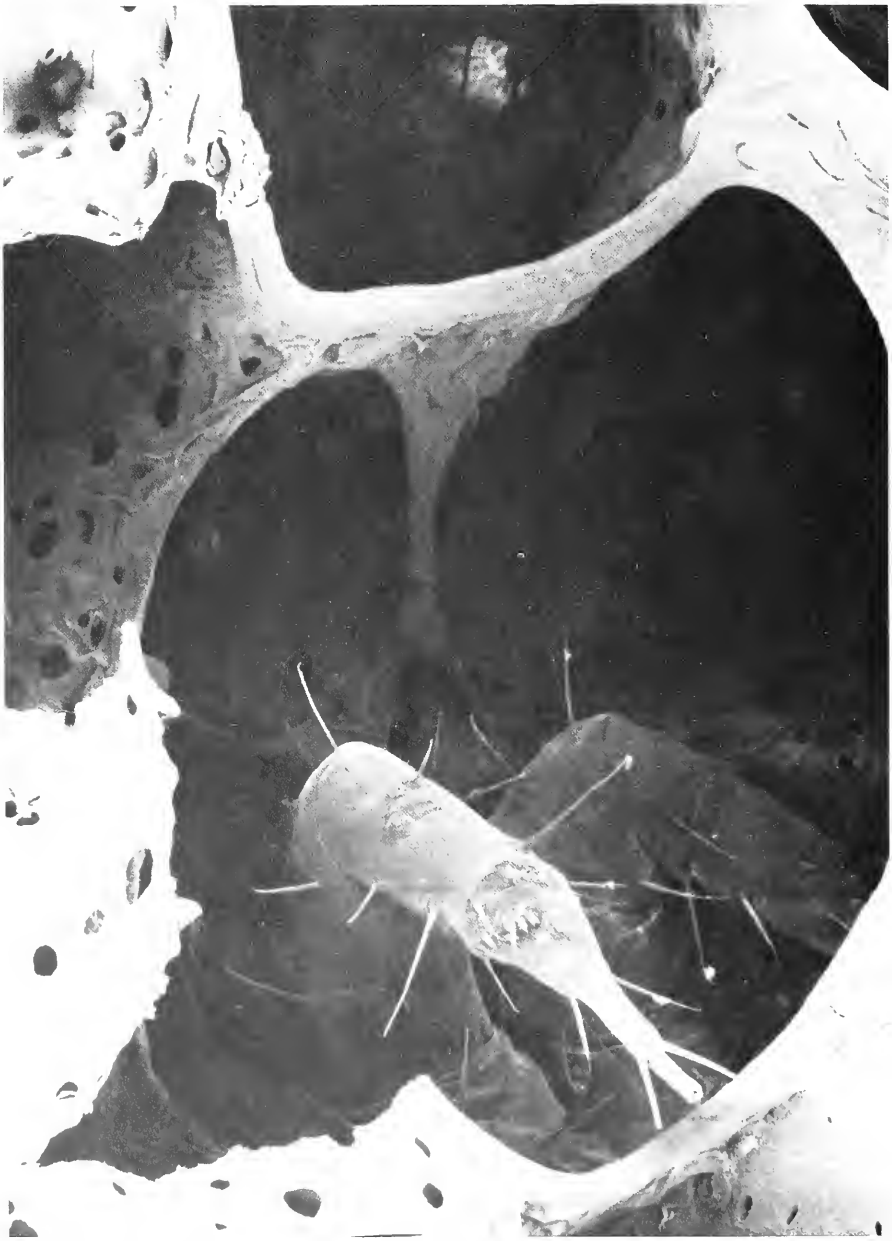
Emphysema and Chronic Bronchitis

Program Goals: 1979-1983

Directed toward the ultimate goal of prevention and control of chronic obstructive lung diseases, the Institute's program seeks to find means to delay or reverse disease progression through greater knowledge of pathogenesis and to ameliorate the morbidity and mortality due to these diseases through improved techniques for early diagnosis and more effective management.

Specific goals to be achieved during the next 5-year period are:

- Characterize presymptomatic stages of chronic obstructive lung diseases and determine if such changes are reversible.
- Identify and better determine the relative contribution of risk factors such as cigarette smoking and environmental, socioeconomic, genetic, and other host factors to the incidence and exacerbation of chronic bronchitis and emphysema.
- Determine the role of proteases in the development of pulmonary emphysema and assess the role of protease inhibitors in preventing lung tissue damage.
- Reduce the frequency and morbidity of asthma through characterization of disease etiologic and pathogenic processes.
- Evaluate current therapeutic regimens for chronic obstructive lung disease in terms of their efficacy, cost, and indications, and develop new therapeutic interventions based on an improved understanding of pathophysiology.



A micrograph of a lung mite, a parasite found in the lung of a rhesus monkey, was produced by a scanning electron microscope. The clinically undetectable invader is enlarged 265 times.

Research Activities: 1979-1983

Capitalizing on the momentum achieved to date in progress toward prevention and control of chronic obstructive lung disease, research activities over the next 5-year period will principally carry forward ongoing projects.

Continuing research efforts include:

- Longitudinal studies of the natural history of chronic bronchitis and emphysema, emphasizing when in the course of the disease deleterious changes can be arrested or reversed through therapeutic interventions.
- Investigations of pulmonary function tests that detect presymptomatic stages of chronic obstructive lung disease.
- Investigations of pulmonary function in individuals identified as heterozygous for alpha-1-antitrypsin deficiency.
- Efforts to foster use of standardized procedures — pulmonary function tests, respiratory symptom questionnaires, and chest X-rays — in longitudinal and other population studies of chronic obstructive lung disease.
- Studies to correlate biochemical and physiologic alterations in early stages of chronic obstructive lung disease.
- Characterization of the mediators involved in asthma.
- Studies of the efficacy of nocturnal oxygen therapy in chronic obstructive lung disease.
- Studies on the use of intermittent positive pressure breathing for treatment of chronic obstructive lung disease.

Studies to be implemented:

- Programs to determine changes in pulmonary function in individuals participating in smoking cessation programs.
- Studies to reduce frequency and morbidity of asthma through characterization of the etiology and pathogenesis of the disease process.
- Evaluation of the relative efficacy and cost of various therapeutic and rehabilitative techniques to manage chronic obstructive lung disease.

Studies under consideration for increased support:

- Population studies to quantify the relative roles of various risk factors — cigarette smoking, environmental, socioeconomic, genetic, and other host factors — in the etiology of chronic obstructive lung disease.
- Role of proteases in development of pulmonary emphysema and the assessment of protease inhibitors in preventing lung tissue damage.

Pediatric Pulmonary Diseases

Program Goals: 1979-1983

Working toward the prevention of pediatric pulmonary diseases through increased knowledge of the underlying disease process, the Institute plans to achieve the following specific goals during the next 5-year period.

Respiratory Distress Syndrome of the Newborn:

- Determine maternal, developmental, and environmental factors that increase risk of respiratory distress syndrome of the newborn.
- Characterize the clinical, pathological, physiologic, biochemical and molecular events associated with the onset and cause of the disease syndrome.
- Determine if subsequent development is impaired in children who recover from respiratory distress syndrome of the newborn.

Cystic Fibrosis:

- Identify cystic fibrosis factors in patients and genetic markers in heterozygous carriers of the cystic fibrosis gene.
- Elucidate normal mechanisms involved in mucociliary clearance and determine how these are modified in cystic fibrosis.
- Develop therapies and procedures for management of patients with cystic fibrosis.

Bronchiolitis:

- Characterize the pathologic, immunologic, and physiologic manifestations associated with the onset and course of bronchiolitis.
- Evaluate the role of bronchiolitis in subsequent disorders of the airways and lung parenchyma.

- Assess the role of genetic, immunologic, developmental, and socioeconomic factors that may be related to the occurrence and severity of bronchiolitis.

Research Activities: 1979-1983

Respiratory Distress Syndrome of the Newborn

Prenatal assessment of lung maturity by analysis of the amniotic fluid now makes feasible the earliest possible care of newborns with hyaline membrane disease. Further research, as indicated below, is needed to advance both prevention and treatment.

Continuing research efforts include:

- Investigations to characterize the clinical, pathologic, physiologic, biochemical, and molecular events associated with normal lung development and the onset and course of respiratory distress syndrome of the newborn.
- Trials of the efficacy of antenatal administration of steroids in prevention of respiratory distress syndrome of the newborn.

Studies under consideration for increased support:

- Investigations of maternal, developmental, and environmental factors that increase risk of respiratory distress syndrome of the newborn.
- Research to determine if subsequent development is impaired in children who recover from respiratory distress syndrome of the newborn.

Cystic Fibrosis

Continuing research efforts include:

- Studies to identify cystic fibrosis factors in patients, and genetic makers in heterozygous carriers of the cystic fibrosis gene.
- Studies to identify pulmonary cells or tissue site damaged or altered during the various stages of cystic fibrosis with emphasis on the earliest detectable structural changes in lung tissue.

Studies under consideration for increased support:

- Investigations to elucidate normal mechanisms of mucociliary clearance and to determine how these mechanisms are modified in cystic fibrosis.

Bronchiolitis

Studies to be implemented:

- Research to characterize the pathologic, immunologic, and physiologic manifestations associated with the clinical onset and the course of bronchiolitis.
- Investigations of the role of genetic, immunologic, developmental, and socioeconomic factors relevant to the occurrence and severity of bronchiolitis.

Studies under consideration for increased support:

- Research to evaluate the role of bronchiolitis in subsequent disorders of the airways and lung parenchyma.

Fibrotic and Immunologic Diseases

Program Goals: 1979-1983

The overall goals of the Institute in this category of lung diseases are to prevent fibrotic and immunologic lung diseases through better understanding of specific airborne hazards and of the mechanisms by which they induce lung injury, and to improve early detection and clinical management of pulmonary fibrosis due to primary or secondary lung tissue injury.

Specific goals during the next 5 years are as follows:

- Identify specific agents responsible for fibrotic lung diseases and hypersensitivity pneumonitis, and establish dose-to-effect relationships between these agents and resultant lung reactions.
- Determine prevalence of fibrotic lung diseases and hypersensitivity pneumonitis, and characterize their natural history.
- Characterize biochemical, cellular, and immunologic events associated with the clinical onset and course of fibrotic lung diseases and hypersensitivity pneumonitis.
- Reduce frequency of occurrence and develop treatments for primary pulmonary fibrosis and for fibrotic reactions secondary to immunologic lung disease.
- Determine how the autonomic nervous system affects airway caliber of different levels of the bronchial tree in health and disease.

- Determine the role of epithelial damage in the sensitivity of bronchi on exposure to various respiratory irritants and establish the anatomical basis of the abnormalities.
- Determine functions of kinins, their release mechanisms and influence on airway smooth muscle.

Research Activities: 1979-1983

During recent years, the Institute has encouraged a multidisciplinary approach to etiologic, diagnostic, and therapeutic problems posed by fibrotic and immunologic lung diseases. Though much valuable information has been gained, among the vital facts still eluding investigators is what causes the abnormal accumulation of fibrous collagen-containing material in the lungs of patients with these diseases. Hopefully, pursuit of the following research activities will bring these and additional answers during the next 5 years.

Continuing research efforts include:

- Investigations of specific agents responsible for fibrotic lung diseases in specific occupational environments, with specific attention to dose-response relationships.
- Investigations of specific agents responsible for hypersensitivity pneumonitis in working and home environments, with special emphasis on measures to reduce or eliminate exposures.
- Epidemiologic studies of populations exposed to organic dusts that cause hypersensitivity pneumonitis to elucidate the natural history of the disease.
- Development of animal models of fibrotic lung diseases and hypersensitivity pneumonitis.
- Investigations relative to the immunologic and biochemical responses to organic and inorganic dusts that lead to fibrotic lung diseases and hypersensitivity pneumonitis.
- Investigations of the role of the kallikrein-kinin system in the immediate hypersensitivity reaction of asthma.
- Studies of the functional relationship between the autonomic nervous system and airway resistance in the normal and the diseased lung.

Studies to be implemented:

- Population studies to determine the relative contributions of occupational and nonoccupational factors in the occurrence of fibrotic lung diseases.
- Studies resulting in the early recognition and prompt treatment of the pulmonary manifestations of systemic diseases.
- Investigations to increase understanding of agents involved in drug-induced pulmonary disease and to increase recognition of early symptoms.
- Research on the mechanisms by which beta-sympathomimetic agents produce relaxation of bronchial smooth muscle.
- Investigations of the role of epithelial damage in the sensitivity of bronchi upon exposure to various respiratory irritants.

Studies under consideration for increased support:

- Investigations on the role of collagen in the development of pulmonary fibrosis.

Respiratory Failure

Program Goals 1979-1983

To reduce death and disability from respiratory failure, the Institute's overall goal is to improve the diagnosis and management of acute respiratory failure in the adult through better understanding of the structural, biochemical, and physiologic mechanisms of acute lung injury. Specific goals directing the Institute's program during the next 5 years are as follows:

- Characterize the mechanisms involved in lung injury, and identify precipitating factors that result in acute respiratory failure.
- Determine how lung tissue changes associated with acute respiratory failure can be arrested or reversed.
- Develop noninvasive techniques for early detection and continous monitoring of acute respiratory failure.
- Assess the efficacy of current modes of therapy for acute respiratory failure in the adult and develop more effective supportive and curative procedures.

Research Activities: 1979-1983

Research in respiratory failure is now emphasizing disease control as a result of increased knowledge of the fundamental mechanisms of pulmonary

injury, etiology, and the pathogenesis of disease. The Institute's program over the next 5 years is as follows:

Continuing research efforts include:

- Development of noninvasive techniques for early detection and continuous monitoring of acute respiratory failure.

Studies to be implemented:

- Through Specialized Centers of Research, initiation of interdisciplinary approaches to elucidate mechanisms involved in lung injury, identification of precipitating factors that result in acute respiratory failure, determination of how degenerative changes can be arrested or reversed, and improvements in the detection and clinical management of acute respiratory failure in the adult.

Pulmonary Vascular Diseases

Program Goals: 1979-1983

In pulmonary vascular diseases, early detection of disease is the key to effective patient management as increased fundamental knowledge of pulmonary circulation is to effective disease prevention. The overall goals of the Institute with respect to these diseases are to elucidate mechanisms underlying development of pulmonary edema, pulmonary hypertension, and cor pulmonale, and to bring this knowledge to bear on improving the diagnosis and treatment of these disorders.

Specific goals for the next 5 years are as follows:

- Characterize the dynamics of fluid and solute exchange, and the role of vasoactive mediators in the pathogenesis of pulmonary edema.
- Determine the structural, biochemical, and physiologic characteristics of pulmonary vascular smooth muscle, and the roles of hypoxia and vasoactive mediators in the etiology of pulmonary hypertension.
- Develop noninvasive techniques for early diagnosis and continuous monitoring of pulmonary hypertension and pulmonary edema.

Research Activities: 1979-1983

Recent Institute-sponsored research is developing techniques for the detection of early cases of pulmonary hypertension and pulmonary edema. Further work with this methodology will continue, but the principal emphasis of research activities during the next 5 years will be on the basic physiologic and pharmacologic parameters initiating disease and providing effective therapy.

Continuing research efforts include:

- Investigations of fluid and solute exchange in the normal and the diseased lung, including assessment of the effect of vasoactive mediators on the integrity of the pulmonary endothelium.
- Development of animal models of pulmonary edema.
- Development of animal models of pulmonary hypertension and cor pulmonale.
- Development of noninvasive techniques for early detection and continuous monitoring of pulmonary hypertension and pulmonary edema.
- Investigation of the structural, biochemical, and physiologic characteristics of pulmonary vascular smooth muscle.

Studies under consideration for increased support:

- Role of hypoxia and vasoactive mediators in the development of pulmonary hypertension.

BLOOD DISEASES AND BLOOD RESOURCES

Bleeding and Clotting Disorders

Program Goals: 1979-1983

Advances in basic understanding of the coagulation system are critical to reduction of the incidence of disability and death from occlusive arterial and venous thrombosis, to the alleviation of symptoms of hemophilia, and to the development of effective therapy for congenital and acquired platelet disorders. To make these therapeutic improvements a practical clinical reality, the Institute has established four basic goals to guide its research activities for the next 5 years:

- Improve the diagnosis of, and therapy for, arterial thrombosis and the various clinical sequelae of this disease process to bring about its ultimate prevention.
- Enhance the basic knowledge of venous thrombosis to provide improved prophylactic therapy and patient care.

- Develop better understanding of the genetic and pathological mechanisms underlying hemophilia and other bleeding disorders to develop improved diagnostic techniques and specific treatments. For those coagulation disorders which are acquired, not inherited, develop better methods for identifying and detecting individuals at risk.
- Increase the general understanding of the role of platelets in the mechanisms of bleeding and clotting and develop more effective therapy for individuals suffering from congenital and acquired platelet disorders.

Research Activities: 1979-1983

Progress to this time allows the Institute to plan much more specific and targeted research activities for the next 5 years. While the areas of investigation are, in large part, the same as or similar to those determined in 1972, the activities planned for 1979-1983 reflect a more advanced knowledge of the specifics involved in the coagulation system, the molecular action of Factor VIII, the detection of thromboembolic disorders, and the clinical application of anticoagulant therapy.

Continuing research efforts:

- Investigation of the structure and function of protein coagulation factors.
- Determination of the function of Factor VIII and clarification of its role in hemophilia, von Willebrand's disease, and thromboembolic states.
- Studies of the immunologic, epidemiologic, and molecular mechanisms through which hemophiliacs develop inhibitors to Factor VIII.
- Research on the biochemistry, structure, and function of the platelet and on the phenomena related to platelet production.
- Studies to correlate *in vitro* platelet function testing and *in vivo* platelet function.
- Further elucidation of the mechanisms of action of prostaglandins and thromboxanes to determine how the metabolites of arachidonic acid control platelet function.
- A search for drugs which affect platelet action and inhibit thrombosis.
- Evaluation of the clinical use of anticoagulants and development of professional educational efforts regarding their proper usage.
- Consultation to the Health Services Administration supporting the comprehensive hemophilia clinics and collection of clinical data from these clinics.
- Support for animal models of hemophilia and thrombotic disorders.

Studies to be implemented:

- Investigations designed to clarify biosynthesis of the coagulation factors.
- Clarification of the role of prothrombin complexes in the treatment of patients with Factor VIII inhibitors and identification of the procoagulant substances in these concentrates.
- Standardization of the platelet function tests, using the proceedings of a workshop on this subject held in late 1977.
- Clarification of the role of the thrombotic process in atherogenesis.
- Assurance of an adequate supply of animals with hemostatic defects for basic studies on atherogenesis with emphasis on those with von Willebrand's disease.

Studies under consideration for increased support:

- Kinetic investigations of coagulation factors and regulatory mechanisms involving application of the knowledge gained in purified protein systems to whole animal or whole cell systems.
- Determination of whether patients with von Willebrand's disease are protected from atherosclerosis.
- Clarification of the clinical pattern of hemophilia, including medical, social, psychologic, and economic factors.
- Elucidation of the interaction between the platelet, Factor VIII, and the vessel wall.
- Investigation of methods of culturing cells of importance to hemostasis including megakaryocytes, endothelial cells, and liver cells.
- Investigation of the factors regulating blood vessel growth and proliferation.
- Studies of the interrelations of diet, platelet function, and atherosclerosis with emphasis on the relationship to arachidonic acid metabolism.
- Investigation of the antithrombin system including chemical, cellular, and physiologic aspects with emphasis on the importance of this system in the regulation of hemostasis and thrombosis.

Red Blood Cell Disorders

Program Goals: 1979-1983

The overall goal of the program for the next 5 years is the development of new knowledge relevant to improving patient treatment, and to extending the lifespan of those afflicted with thalassemia, aplastic anemia, and refractory anemia as well as improving the health status of those afflicted with the various hemolytic anemias. Specific goals are to:

- Devise improved treatment for those already afflicted with thalassemia. Major effort will be devoted to identification of carriers through effective screening.
- Develop knowledge of the underlying causes of aplastic and refractory anemias to permit improved treatment; develop information concerning the natural history of these diseases.
- Further elucidate red cell membrane structure, function, and intracellular metabolism to provide information which may be utilized to improve the health status of patients afflicted with the various hemolytic anemias.
- Improve overall knowledge of the crucial role of the red blood cell in oxygen transport through studies of the mechanisms of control of oxygen exchange.
- Develop erythropoietin preparations suitable for use in controlling human diseases.

Research Activities: 1979-1983

Advances during the past 5 years have not only contributed to our capability to define much more specific areas for targeted research but place us at the point where investigations can lead to improved methods for control and prevention of red blood cell disorders.

The 5-year projections listed below represent our current state of knowledge and the most promising avenues for targeted research. As investigations progress, new initiatives will surely evolve and be incorporated into this plan.

Continuing efforts:

- Studies of the molecular and clinical aspects of thalassemia, especially the use of iron-chelating agents.
- *In vitro* and *in vivo* studies of the function and characterization of stem cells.
- Purification and characterization of erythropoietin through application of modern purification techniques.
- Studies of the chemistry and function of the red blood cell membrane.
- Investigations of molecular and nutritional aspects of folic acid and vitamin B_{12}.

Studies to be implemented:

- Utilization of pure erythropoietin to develop and improve assays for clinical use.
- Research on *in vivo* aspects of oxygen exchange at the capillary levels in animals and man.
- Clinical investigations of erythropoietin in selected disorders such as chronic renal failure.

Studies under consideration for increased support:

- Clarification of the significance of various degrees of iron deficiency.
- Application of results of stem cell research to clinical bone marrow transplantation.

Sickle Cell Disease

Program Goals: 1979-1983

To fulfill its mission to reduce morbidity and mortality due to sickle cell disease and to translate state-of-the-science conceptualizations into universal practice, the NHLBI has established the following goals:

- To continue basic research into the pathophysiology of the disease process at the molecular, cellular, and clinical levels.
- To develop improved methods of clinical care.
- To develop a more rational approach to patient management, based on the latest scientific advances.

Research Activities: 1979-1983

Improved clinical management of individuals with sickle cell disease requires a sound basic research program and a concerted effort to educate the practitioner in the community. To this end the program has planned and is already conducting a number of research activities.

Continuing efforts include:

- The elucidation of the intermolecular contacts of the HbS fiber by use of a variety of techniques which include:
  - Fiber X-ray diffraction studies with major emphasis on obtaining fiber patterns with more ordering.
  - Spectroscopic techniques including high-resolution nuclear magnetic resonance and various spectroscopic probe methods.
  - Study of the gelling properties of chemically modified hemoglobin S and genetically modified hemoglobins.
  - Single crystal X-ray diffraction studies to define the three-dimensional structure of the oxy- and deoxy- forms of hemoglobin S.
- Studies on the equilibrium and kinetic aspects of the factors that affect gel formation.
- Development of techniques for studying the mechanisms of the switch from fetal to adult hemoglobin production.
- Molecular studies aimed at the delineation of the regulation of globin gene expression in general as well as the gamma and beta loci specifically.
- Studies to define the cellular regulation of gene activity in differentiating cells.
- Studies on metabolism of sickled cells, such as development of incubation systems which more closely simulate human intravascular and tissue conditions and permit controlled perturbations of pH, pO_2, and temperature.
- Development of new and better inhibitors of polymerization of hemoglobin S.
- Determination of the pathophysiology of sickle cell disease. (While the major abnormality in sickle cell disease is stasis of the red cells in the microvasculature, it is not yet possible to quantify this process.)
- Development of an integrated study to collect uniform data on the clinical course of sickle cell disease.
- Studies to assess the role of coagulation in the pathogenesis of vaso-occlusive crises.
- Evaluation of the use of hypertransfusion therapy both prophylactically and in the treatment of crises.
- Development of safe and effective techniques of fetal blood sampling for the prenatal diagnosis of sickle cell disease.
- Development of extracorporeal techniques for administering drugs to circumvent toxicity and to permit further study of potential drugs in a more controlled manner.
- Evaluation of potential therapeutic agents for sickle cell disease.

Blood Resources

Program Goals: 1979-1983

The mission of the NHLBI in the areas of blood transfusion and transplantation biology is twofold: to assure an adequate supply of high quality blood and blood products to everyone in need, and to advance basic understanding of the immunology and genetics of transplantation biology to improve clinical application. Overall goals flow from this mission and will continue to guide the program's development during the next 5 years. Because this program encompasses five distinct program initiatives, the goals and research activities for each of the five program areas will be reported separately.

National Blood Program:

- Foster the efficient use and assure an adequate supply of high-quality blood and blood products for everyone in need. Promote more effective planning in the management of the national blood resource through the collection and analysis of national blood resource data.
- Improve the management of our national blood resource through studies of currently operating blood procurement procedures, donor recruitment strategies, current manpower training needs, dynamics of regional supply systems, and methods for promoting the safety of blood service operations.

Blood Safety Program:

- Prevent morbidity and mortality from post-transfusion hepatitis and other transfusion-transmitted infections.
- Eliminate toxic substances from the many surfaces contacted during the collection, processing, storage, and transfusion of blood.
- Produce a universally acceptable system to ensure that the patient receives the designated transfusion.

- Eliminate human errors through the development of automated blood typing and cross-matching instrumentation.

Blood Substitutes Program:

- Synthesize and biologically screen new and improved fluorocarbon compounds for use as artificial blood substitutes.
- Synthesize and test iron-chelate complexes for use in artificial blood substitutes for eventual complete replacement *in vivo* or for the perfusion of isolated organs *in vitro*.
- Develop the surfactants necessary to effectively emulsify those classes of fluorocarbons showing greatest potential as blood substitutes.
- Study the biological effects of perfluorinated substances as artifical blood substitutes.

Blood Component Therapy Program:

- Develop definitive guidelines for the clinical use of platelet concentrates for transfusion.
- Determine and clarify parameters of collection and function of leukocytes as related to effective transfusion therapy.
- Clarify guidelines relative to proper use of red blood cells, to maximize their use in place of whole blood where appropriate.
- Develop new methods of plasma fractionation including the preparation of clinically useful trace components. Support clinical trials for FDA licensure of these new components and methods.

Transplantation Biology Program:

- Support activities for testing cells and tissues aimed at clinical application of histocompatibility.
- Collaborate with other institutes in the maintenance of a national HLA-type registry.

Research Activities: 1979-1983

Each of the five program areas listed above has developed a detailed plan of research activities directed toward realizing its goals. These activities are listed by program below.

National Blood Program

Continuing research efforts include:

- The Task Force on "Operating Relationships and Resource Sharing of Blood Banking Services on a Regional Basis."
- The Task Force on "Meeting National Blood Banking Data Needs," through effective planning to promote more efficient use of the national blood supply.
- Development of the National Blood Data Center to collect data on the national blood resource relative to training needs, collection, and utilization of blood and blood products.

Studies to be implemented:

- A study on "Blood Utilization" to encourage the use of blood components or plasma fractions instead of whole blood where appropriate.

Safety of Blood Therapy

Continuing research efforts include:

- The study of transfusion-transmitted viral hepatitis being conducted in five medical centers.
- Maintenance of chimpanzees for hepatitis research.
- A study to evaluate the prophylactic ability and treatment potential of hepatitis B immune globulin (HBIG).
- A study for the removal of hepatitis virus from infectious blood and blood products.
- A study of improved hepatitis detection.
- A study using hepatitis B immune globulin to interrupt the transmission of hepatitis from mother to fetus.

Studies to be implemented:

- Evaluation of the effectiveness of E antigen as a "marker" of hepatitis infectivity.
- Initiation of new studies on the epidemiologic, clinical, and serologic characterization of non-A, non-B hepatitis, the most common cause of post-transfusion hepatitis.
- Development of a new procedure to assure the positive identification of compatible blood for patients.
- Research to determine whether freezing and/or washing of red blood cells will lower the incidence of hepatitis in transfused patients.

Blood Substitutes Program

Continuing research efforts include:

- Synthesis and biological screening of new and improved fluorocarbon compounds for use as artificial blood substitutes.

- Testing, in small animals, the effectiveness of new fluorocarbons as temporary blood substitutes.
- Development and testing of oxygen-binding chelates in animals with much of their blood replaced by free hemoglobin.

Studies to be implemented:

- Development of new surfactants necessary to effectively emulsify newly synthesized clinically useful fluorocarbon compounds.
- Research on the biological effects of perfluorinated substances used as artificial blood substitutes.

Blood Component Therapy

Continuing research efforts include:

- Studies on the preservation of human platelets for transfusion.
- Studies on the collection, function, and transfusion of platelets.
- Studies on the collection, function, transfusion of granulocytes. The results of these studies will be used to develop clinical guidelines for optimal transfusion therapy.
- Development of new methods of plasma fractionation.

Blood Substitutes Program

Studies under consideration for increased support:

- Studies to examine parameters of filtration and centrifugation systems that affect yield and function in the procurement of leukocytes.
- Studies to determine the effect of leukophoresis on repeat donors to establish guidelines to assure donor safety and to assist in donor selection.

Transplantation Biology

Continuing research efforts include:

- Basic research in transplantation (HLA) antigens to determine the role and relevance of the antigens for bone marrow and renal transplantation and platelet and/or granulocyte transfusions.
- Studies to provide new methods potentially capable of making blood products "free" of leukocyte antigens.
- Development and production of B lymphocyte typing sera as part of the national blood resource.

VII.
Resource Allocations

GROWTH OF RESPONSIBILITIES

New legislation in 1972 and 1976 increased NHLBI's mandated responsibilities to support research in heart, lung, blood diseases, and blood resources. In response to these expanded mandates, NHLBI has initiated new programs and expanded existing ones. This expansion, as well as the opening up of new fields for scientific investigation, has vastly increased the size of the Institute's scientific community as well as the number, diversity, and complexity of research proposals submitted.

Since 1972, NHLBI's mandate has expanded greatly. Congress has given the Institute new responsibilities in the areas of:

- Lung Diseases
- Sickle Cell Disease
- Clinical Trials
- High Blood Pressure Education
- Blood Diseases
- Research and Demonstration Centers
- Prevention, Education, and Control
- Blood Resources.

Each year NHLBI receives more and more scientifically worthy research proposals. Unfortunately, the number of creative and meritorious proposals far exceeds the Institute's ability to fund them. As the continuing record of research accomplishments attests, the Institute does not lack either commitment or opportunity to keep pace with the rapid progress of scientific knowledge, but the Institute does lack sufficient resources and professional staff to fully implement the National Program.

To carry out its mandated responsibilities, the Institute's resources must keep pace with both inflation and advances in the sophistication of scientific methodologies. In 1972, the first year of the passage of the National Heart, Blood Vessel, Lung, and Blood Act, the Institute's obligations amounted to $232.6 million (in actual dollars). By 1978, NHLBI dollar obli-

gations had risen to $447.9 million. In view of inflation, in terms of constant 1972 dollars this would correspond to only $302 million using the standard cost of living scale. However, it is recognized that medical care costs have risen at a rate considerably in excess of the overall costs of living; this is also reflected in the cost of medical research. Thus, actual dollar power increased minimally despite the continued great increase of responsibilities since 1972 (see figure 7).

Even though the Institute's responsibilities have grown steadily, NHLBI's share of overall NIH resources has not increased. The NHLBI percentage of total NIH research funds has remained essentially constant, fluctuating between 16 percent and 17 percent since 1970.

The Institute's inability to fund many worthy research proposals is especially concerning. The number of competing regular research grant applications submitted and reviewed has grown substantially from 1,154 in 1972 to 1,921 in 1978 (table VI and figure 8). Some of this increase can be attributed to the Institute's expanded mandate, but much of it is a reflection of the growing scope of research opportunities. Over these years the number of grants approved increased as well, but because of limitation in funds, the fraction of approved grants which could actually be awarded diminished significantly from 62 percent in 1972 to only 45 percent in 1978 (table VI, figure 9).

Table VI

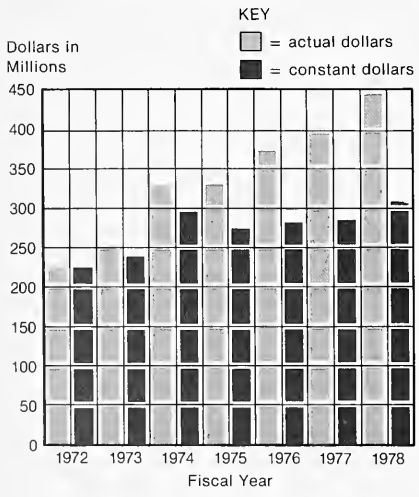
Trends in NHLBI Investigator-Initiated Research: Competing Regular Research Grants[1]

Year	Reviewed	Approved	Awarded	% of Approved Grants Awarded
1972	1154	753	467	62
1973	1255	887	405	46
1974	1463	1084	573	53
1975	1438	1084	568	52
1976	1495	1081	648	60
1977	2040	1416	646	46
1978	1921	1464	665	45

[1] Includes regular research grant applications (R01's—types 1, 2, 3, and 9).

Figure 7

NHLBI Obligation Summary for 1972-1978 Actual and Constant Dollars



This figure uses Inflation Factors in the Feb. 1978 Memo of Dr. Herbert Wooley, NIH, as follows: 1972-1,000; 1973-1,047; 1974-1,108; 1975-1,215; 1976-1,328; 1977-1,413; 1978-1,483.

Figure 8

Trends in NHLBI Investigator-Initiated Research: Competing Regular Research Grants

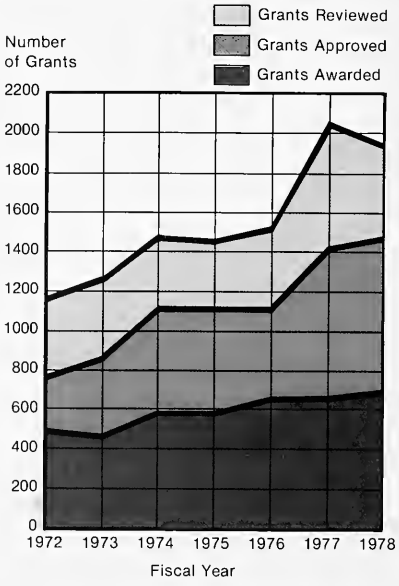
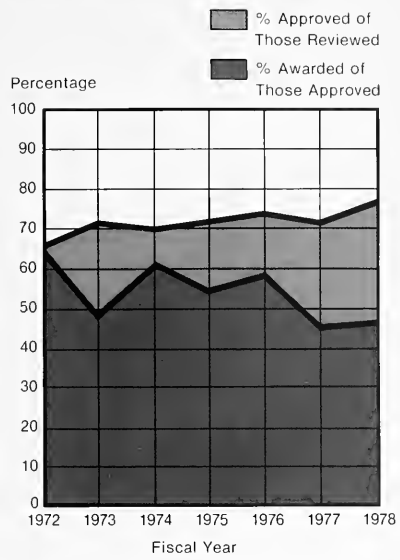


Figure 9

Approval and Award Rate of NHLBI Competing Regular Research Grants



The resources applied to the research grant program have increased substantially, with direct costs rising from $81.4 million in 1972 to $157.7 million in 1978 (table VII). However, the indirect costs accompanying these grant awards have risen even more steeply from $25.0 million in 1972 to $59.1 million in 1978.

In any consideration of Institute resource allocation, it must be remembered that almost all projects supported by the Institute are multiyear activities. Thus, to continue the activities already ongoing and committed requires a large fraction of Institute funds, and only a small fraction is available for the competitive renewal of existing projects and the initiation of new activities.

All of these factors combine to place serious constraints upon NHLBI activities and force the Institute to choose very carefully among competing priorities. Unfortunately, there are now many approved research grant applications of significant merit which NHLBI cannot support; there are important targeted initiatives which the Institute cannot undertake because of the tight competition for its funds. Increased mandated responsibilities, inflation, the increasing commitment base, the increased number of grant applications, the growth of direct research costs necessary for the conduct of research, and the steadily climbing indirect costs all make it impossible for the NHLBI to fund an adequately large fraction of high priority investigator-initiated projects.

PROJECTED RESOURCE NEEDS

NHLBI bases its projection of resource needs on a critical review of the state of the science, future research opportunities, planned initiatives, ongoing commitments, and specific estimates of resource needs of planned activities. This critical review involves both scientific and professional assessment

Table VII

Growth of Indirect Cost Rates of Research Grants,[1] Fiscal Years 1972-1978

Fiscal	Direct	Indirect	Indirect Cost as a Percentage of Direct Cost	Total Cost
1972	$ 81,350,199	$25,035,497	30.8	$106,385,696
1973	86,539,991	27,674,325	32.0	114,214,316
1974	109,691,890	37,797,863	34.5	147,489,753
1975	101,970,760	36,288,184	35.6	138,258,944
1976	124,915,900	44,436,926	35.9	168,352,826
1977	142,110,745	51,021,715	35.9	193,132,460
1978	157,696,047	59,122,100	37.5	216,818,147

[1] Includes regular project grants, program project grants, and sickle cell centers. Excludes R09, R13, and P09 grants, Research and Development Centers, and SCOR's.

of the fiscal resources, personnel, and time required to sustain progress and accomplish National Program objectives.

The resource allocations presented in table VIII represent resources needed to carry out the program activities projected in this report. In accordance with legislative requirements, at least 15 percent of the fiscal resources are allocated for diseases of the lung and at least 15 percent are allocated for blood diseases and blood resources.

The National Program is projected to require an estimated total of $635.5 million in 1980, increasing to $825.1 million in 1984. To fully implement the National Program, the requested resources represent a substantial increase over current resources. However, with the exception of manpower resource projections, the estimates in this report are only slightly different from those projected in the fifth Director's report.

While the National Program Plan section provides greater detail concerning program plans, the rationale for the resource projections is as follows:

- *Investigator-Initiated Research Program* — Because of resource limitations and the desire to maintain a vital investigator-initiated research program, other important areas of the National Program have been limited. NHLBI cannot overemphasize the fact that the cost and number of research grant applications have grown markedly, and that the growth in funds available for support has not kept pace. This has prevented the funding of a large percentage of approved meritorious applications. Table VIII estimates funds needed to meet the increasing research needs.

- *National Research and Demonstration Centers* — These centers will continue to hasten the process by which research advances are validated and applied to improve community health care. The projected budget provides for another center competition in FY 1980, and for an expansion of the Program in 1982.

- *Prevention, Education, and Control Programs* — Through coordinating the efforts of voluntary, professional, and civic organizations, a variety of projects has been undertaken. With the termination of the Institute's current primary prevention trials, the FY 1983 projected figures reflect an expected increase in associated prevention, education, and control programs.

- *Construction* — The National Heart, Lung and Blood Advisory Council has emphasized the need for research facilities construction. Budget projections take into account the costs of constructing facilities to meet this important need.

- *Training* — The long-range research, education, and demonstration programs previously discussed and the growing sophistication in the heart, lung, and blood field require increased training and manpower development. The FY 1982 budget projection reflects an increased program to attract physicians into research. This is needed to offset the steady decline over the past 6 years in the number of physician investigators.

- *Intramural Research* — Development of the proposed Ambulatory Care Facility requires modest increases in Intramural Research Program resources from 1978 through 1983.

An alternative, lowerbound budget is presented in table IX. This plan would delay the funding of Institute-solicited research programs, i.e., research grants and contracts in areas of opportunity identified by the NHLBI. It would defer funding of additional centers and limit the number of new centers. Growth of prevention, education, and control programs would be sharply limited. Funds for construction would be eliminated; the budget for training would be reduced; and there would be modest decreases in the intramural research program. The research management and program services budget would be adjusted accordingly.

NHLBI STAFF ALLOCATION PLAN

Since the enactment of the Institute's new legislative mandate in 1972, the NHLBI has suffered a personnel shortage. In response to the Act, the Institute has initiated activity in a number of new areas. Many new programs, especially the many clinical trials and targeted activities, require a high ratio of manpower to dollars. To operate the National Program effectively, the NHLBI needs additional staff at both the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education and comprehensive centers are new to the National Institutes of

Table IX

Projected Resource Allocation[1] for the National Heart, Blood Vessel, Lung, and Blood Program, Fiscal Years 1980-1984 (dollars in millions)

	1980	1981	1982	1983	1984
Extramural Research Programs					
Heart and Vascular Diseases	$250.0	$253.0	$270.0	$290.0	$298.0
Lung Diseases	65.0	66.6	72.6	85.6	93.6
Blood Diseases and Resources	69.0	70.9	78.9	88.5	95.6
National Research and Demonstration Centers	43.0	43.5	82.5	85.0	89.0
Prevention, Education, and Control Programs	48.0	53.0	55.0	60.0	70.0
Training	40.0	43.0	55.0	60.0	65.0
Construction	35.0	35.0	0	0	0
Total Extramural Research Programs	$550.0	$565.0	$614.0	$669.1	$711.2
Intramural Research	45.9	46.6	50.8	53.8	58.9
Direct Operations and Program Management	39.6	41.4	47.0	49.0	55.0
Total	$635.5	$653.0	$711.8	$771.9	$825.1

[1] These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

Table VIII

Projected Lowerbound Resource Allocation[1] for the National Heart, Blood Vessel, Lung, and Blood Program, Fiscal Years 1980-1984 (dollars in millions)

	1980	1981	1982	1983	1984
Extramural Research Programs					
Heart and Vascular Diseases	$248.8	$251.6	$251.2	$255.3	$275.9
Lung Diseases	64.4	65.9	68.6	73.6	79.6
Blood Diseases and Resources	68.9	69.9	72.2	76.9	83.8
National Research and Demonstration Centers	8.8	11.8	12.6	14.0	15.5
Prevention, Education, and Control Programs	40.0	42.9	45.4	46.8	50.0
Training	33.5	35.9	37.9	42.3	45.6
Construction	0	0	0	0	0
Total Extramural Research Programs	$464.4	$478.0	$487.9	$508.9	$550.4
Intramural Research	44.5	45.0	46.5	47.0	49.9
Direct Operations and Program Management	38.6	40.5	42.5	44.0	46.0
Total	$547.5	$563.5	$576.9	$599.9	$646.3

[1] These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

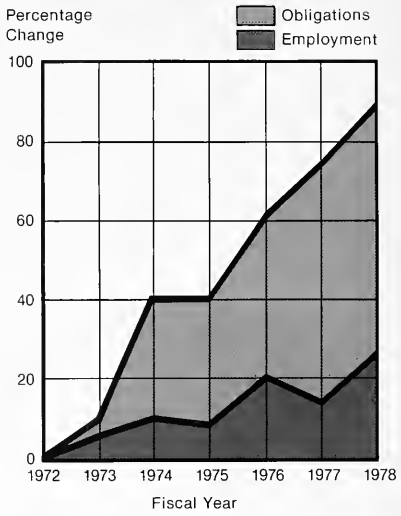
Health. Their review, administration, and evaluation require new staff with different knowledge and skills than those previously available within the Institute. Since these programs require substantially greater staff involvement in comparison with regular grants, manpower needs are particularly intense.

To initiate these extensive new programs within the available manpower resources, the Institute has conserved manpower in several ways. The Division of Technological Applications was abolished and its activities divided among the three categorical scientific divisions. The review function for programs supported by the grant and contract mechanism were centralized, and a number of top-level personnel took on dual organizational functions. Staff was taken from established ongoing programs to meet new program needs. This latter technique, however, has now exhausted all ongoing program flexibility and has left the Institute staff perilously overdeployed.

Figure 10 compares the percentage increase in NHLBI obligations to the percentage increase in employment between 1972 and 1978.

Figure 10

Percentage Change in Obligations and Employment, 1972 to 1978



VIII.
Training and Manpower Development Programs

PRESENT NEEDS

Research training and manpower development are vital to fulfilling the NHLBI mission. Indeed the successful fulfillment of the Institute's mission depends upon well-trained research scientists and clinicians who are committed to fundamental and clinical research areas.

Within the constraints of available resources, the NHLBI has been dedicated to training more investigators in research areas related to cardiovascular, pulmonary, and blood diseases. Despite these efforts, the number of individuals trained declined from 1,433 in 1971 to 1,159 in 1977. Although this trend seems to reverse in 1978 as the number of trainees increased to 1,319, a major drop in trainees is anticipated in 1979 because of the training appropriation being a continuing resolution based upon the FY 1978 funding.

The total number of trainees is deceptive, however. During the years cited, the mandate of the Institute has grown greatly. Actually, the number of trainees in the heart and vascular diseases areas has decreased from 1,111 in 1972 to 857 in 1978.

Even more significantly, the number of trainees who are clinical investigators — i.e., trainees with an M.D. degree — has declined from 630 in 1972 to 226 in 1978. In view of the importance of clinical investigation and the growing mandate for clinical applied research and transfer activities as well as basic investigation, the diminishing fraction of clinical investigators is a topic of serious concern.

PROGRAMS AND AWARDS

National Research Service Awards

The National Research Service Award (NRSA) Act of 1974 repealed previous NHLBI research training authorities. Hence, earlier fellowship and training

programs have been phased out and replaced by NRSA's for individual postdoctoral fellowships and institutional research training fellowships. Individual NRSA fellowships are awarded to beginning postdoctoral scientists, particularly in specified research areas where a documented need for trained manpower exists. The institutional research training fellowships are awarded to eligible institutions which in turn select and train postdoctoral and, in special instances, predoctoral candidates in specific research areas.

In the Division of Heart and Vascular Diseases, the specific need areas are epidemiology, biostatistics, behavioral sciences, population genetics, nutrition, and other multidisciplinary areas related to heart and vascular diseases. The broad area of interest in the Division of Lung Diseases includes investigation of the normal and diseased lung and improved methods of prevention, diagnosis and treatment. The areas of particular interest within the Division of Blood Diseases and Resources include blood resources and blood banking, thrombosis and hemostasis, and red cell disorders, including sickle cell disease and thalassemia.

NHLBI Manpower Development Programs

These programs are designed to meet manpower development needs and also to respond to the requirements and opportunities of recent legislation. Thus, some manpower development programs are funded as training while other, more advanced programs are funded in conjunction with research grants.

- *Research Career Development Award (RCDA) Program* — Initiated by NIH in 1961, this program finances 5-year stipends for individuals of high promise with at least 3 years of postdoctoral training, who have demonstrated their capacity for independent research but who have not yet attained recognition as established investigators. The objective is to enhance the recipients' scientific research careers by freeing them from most of their other academic obligations.

- *Minority Biomedical Support Program* — Through this cooperative program, which is administered by the NIH Division of Research Resources, the NHLBI encourages research participation by ethnic minority faculty, students, and investigators. The research supported during Fiscal Year 1978 included such diverse areas as red cell structure and function, pharmacology of tissues from the lung, and the toxicity of photochemical reaction products of freons on the respiratory system. NHLBI investment in this program has risen from $113,696 in 1975 to $1,397,921 in 1978.

- *Minority Access to Research Careers (MARC) Program* — This program, which is administered by the National Institute of General Medical Sciences, is designed to train minority scientists and teachers in the biomedical field. Included in this program are the MARC Faculty Fellowship Program, providing advanced research training for minority faculty members of 4-year colleges, universities, and health-professional schools with substantial minority student enrollment, and the MARC Visiting Scientist Award, providing financial support for minority visiting scientists. NHLBI support of MARC has grown from $16,000 in 1977 to $41,148 in 1978.

- *Minority Hypertension Research Development Summer Program* — Initiated in 1976, this program enables minority faculty and graduate students to work in research areas related to hypertension at institutions with demonstrated excellence in that field. The goals of the program are to encourage students to enter research fields related to hypertension and to stimulate faculty members to develop a hypertension program (or a similar program in another biomedical area) when they return to their own institutions. In terms of both the number of faculty and students enrolled and the quality of research achieved, the program has been highly successful. During the past year alone, 24 graduate students and 123 faculty were enrolled in the program at 13 minority research institutions.

- *Special Emphasis Research Career Awards (SERCA) in Diabetes Mellitus: Cardiovascular, Metabolic, and Endocrinologic Aspects* — The first seven awards under this new program were made in 1978, four supported by the NHLBI and three by the National Institute of Arthritis, Metabolism, and Digestive Diseases. SERCA encourages a multidisciplinary approach by enabling individuals to study several fundamental and clinical scientific disciplines important for research in the metabolic, endocrinologic, and cardiovascular aspects of diabetes mellitus.

- *National Pulmonary Faculty Training Program* — The goal of this program is to strengthen pulmonary medical faculties by training junior faculty

Student researchers supported by the NHLBI Minority Biomedical Support Program are given a "firsthand" introduction to the career opportunities at NIH.

members at specialized medical centers. The first recipients were selected for training in 1976, and last year 21 trainees were supported at six national training centers.

- *Pulmonary Academic Award Program* — Interest in this program remains high and encourages medical students to pursue studies in respiratory medicine and diseases. An Educational Planning Workshop for Pulmonary Academic Awardees, held on May 11-12, 1978, in Boston, was well attended and highly successful. A large portion of the program is devoted to providing senior staff for pulmonary disease curriculum development and research, and the program also supports students at 45 medical schools throughout the country.

FUTURE PROSPECTS AND PLANS

During the past fiscal year, existing training and manpower development programs were evaluated and recommended for expansion. The Institute and its Advisory Council gave considerable thought to the problem of the decreasing number of physicians going into research careers. To counteract present problems in training and manpower development, such as the current stipend levels, the NRSA payback provision, the taxability of NRSA awards, and the general instability of funding for research training, new programs are being considered. They include a clinical investigator's award and special awards for research training during medical school and/or before specialty training. To fill a special need, preventive cardiology academic awards modeled after the pulmonary academic awards are being initiated.

The NHLBI continually analyzes its training and manpower program to determine and meet critical needs as they arise. Meeting the challenge of the Institute's mission to progress in the prevention and control of cardiovascular, pulmonary, and blood diseases, and in the availability of an adequate and safe blood supply, requires enlarged, flexible manpower and training programs supported by adequate resources.

IX.
National Program Coordination

While the mission of NHLBI is to provide leadership for the National Program to combat heart, lung and blood diseases, a primary responsibility of this leadership is to coordinate activities with other groups working in related areas. Scientists, professional societies, voluntary and other private organizations and individuals collectively form an extensive health community which cooperates actively in the planning, evaluation, implementation and coordination of the National Program. This integrated community assists NHLBI, as NHLBI assists other organizations in carrying out a truly national and interactive effort.

Almost 50 Federal organizations conduct or support programs related to the national effort, ranging from basic biomedical research, health services research and delivery, health care financing, and health resources development, to the evaluation and regulation of these activities. Moreover, there are many private sector efforts such as those of pharmaceutical manufacturers, insurance companies, voluntary organizations, universities, and private practitioners, all of which must contribute to and make use of research and technical developments. NHLBI seeks to bring together the skills, experience and creativity of this wide variety of institutions and individuals. A very important aspect of this combination is the speeding of technology transfer.

COORDINATION STRATEGY

The strategy to fulfill the NHLBI coordinating mission includes numerous mechanisms individually selected to take into account the needs of particular scientific undertakings or configurations of participants. Some of these formal coordinating mechanisms are described in the following section. Section X further describes some coordinating activities on an international scale. Though these two sections begin to suggest the formal mechanisms NHLBI uses, one must first keep in mind the single most important coordinating activity in which the Institute engages: encouraging and arranging direct scientific exchanges among individuals.

The keystone of NHLBI's coordinating activities is participating in and promoting direct contacts between scientists, clinicians, administrators, and other interested individuals. The Institute's many programs and activities annually provide thousands upon thousands of opportunities for individual contacts. More formal mechanisms only begin to tell the story. They cannot describe the excitement that happens when a room full of representatives, two investigators from different regions of the Nation, or two experts in different disciplines suddenly reach that special point in a dialogue when their combined knowledge is shared, and in the sharing a new hypothesis, a new clinical application, or a new scientific theory is generated.

The more formal mechanisms NHLBI uses to encourage scientific interchange and enhance coordination and cooperation include:

- Interagency agreements and interagency collaboration;
- The Interagency Technical Committee (IATC);
- Participation in collaboration efforts sponsored by other organizations; and
- Planning and assessment task forces.

These mechanisms not only help NHLBI to assess its own research directions, but also aid in transferring scientific findings into clinical practice.

INTERAGENCY AGREEMENTS AND INTERAGENCY COLLABORATION

Interagency agreements are formal contractual agreements between NHLBI and other Federal governmental units. Each agreement has defined scientific objectives and spells out the methods that will be used and the respective roles of the cooperating organizations. Two examples of ongoing interagency agreement projects are described below.

Blood Substitutes

The NHLBI/National Aeronautics and Space Administration (NASA) interagency agreement for testing of blood substitutes is a good example of a project in which organizations are working together to attain their mutual objectives. Blood substitutes have substantial potential value in health care for emergency mass transfusion needs, for backup at isolated hospitals, and potentially even wider and more common uses. However, additional basic and applied research are essential.

The NHLBI has entered the second year of a 2-year agreement with NASA for the synthesis and evaluation of new fluorochemicals for use as blood substitutes. In the first year of the program, the means to synthesize hybrid compounds were developed and 13 new compounds were synthesized. Now, in the second year, 20 additional compounds are being developed, and toxicity levels and other tests are under way on mice and other mammals. NHLBI is providing financial support in this endeavor, and NASA is conducting the investigations.

Prehospital Emergency Care for Cardiovascular Patients

Another very productive interagency agreement, between NHLBI and the National Highway Traffic Safety Administration (NHTSA) of the Department of Transportation (DOT), has focused on assessing the state of the art of prehospital emergency care. This agreement is in its first phase, during which important information on specific aspects of cardiovascular emergency treatment is being collected. Earlier research results have indicated that early intervention in cardiovascular episodes by trained medical or lay personnel is of vital importance in preventing sudden cardiac death. Advances in emergency medical systems over the past decade provide early response and continued high-quality care until the patient receives advanced life support or is admitted to an acute-care facility. Concurrent with advances in emergency medical services, there has been a 16.3 percent drop in cardiovascular disease death rates between 1970 and 1976. Some feel that a substantial portion of this decline is attributable to improved emergency medical services.

In the long range, NHLBI and DOT wish to determine the effects that improvements in emergency medical systems have had on cardiovascular care and to identify areas where research may improve the prognosis for patients with acute cardiovascular problems. In the first phase of the NHLBI/DOT agreement, specific short-range objectives are being pursued. The project is identifying, comparing and analyzing many U.S. studies of emergency and prehospital cardiovascular care; it is specifying the data collection requirements for estimating the effects of emergency medical systems on prehospital cardiovascular care; and it is identifying ongoing or planned data collection efforts so that redundancy in data collection efforts can be avoided.

First phase data collection has been completed, and it is expected that these data will help NHLBI, DOT, and other agencies to formulate research and development, education, and service programs specifically incorporating improved means of emergency care for cardiovascular patients.

In addition to the type of formal contractual arrangements represented by these examples of interagency agreements, NHLBI has worked with a number of other Federal agencies on specific programmatic needs ranging from laboratory research to patient and physician education. These efforts include the creation of packaged curriculum materials for training emergency medical technicians, a study of the adequacy of the supply of blood coagulation factors needed by hemophiliacs, and major collaborative efforts relating to blood resources. Moreover, scientific conferences and workshops have brought together scientific and professional representatives from Federal agencies and nongovernment institutions who have responsibilities for the conduct or support of basic research and health care delivery.

INTERAGENCY TECHNICAL COMMITTEE AND INTERAGENCY CATEGORICAL WORKING GROUPS

To assist the Director of the NHLBI in coordinating all Federal programs, the 1972 Act established the Interagency Technical Committee (IATC) on Heart, Blood Vessel, Lung and Blood Diseases, and Blood Resources. This committee is required by law to assure the adequacy and technical soundnes of all Federal health programs and activities relating to these diseases, to maintain adequate program coordination and to provide for communication and information exchange. The Director, NHLBI, serves as chairman of the IATC, and the group's members represent Federal departments and agencies with health functions or responsibilities. Sixteen Federal agencies, whose program activities relate to the National Program and range from basic research to health care delivery, participate in the IATC.

As a result of an analysis of the federally supported program efforts, particular problem areas have been identified as targets for concerted attention, and Interagency Categorical Working Groups have been established to address these specific heart, blood vessel, lung, and blood problems.

The following Interagency Categorical Working Groups are currently active:

- Cardiovascular Biomedical Engineering
- High Blood Pressure Control
- Sickle Cell Disease Education
- Nutrient Composition of Foods
- Pediatric Pulmonary Diseases
- Program Impact Analysis
- Smoking and Health.

The following examples point out recent accomplishments of three of these groups.

Cardiovascular Biomedical Engineering Working Group

The Environmental Protection Agency (EPA), NHLBI and others have recently been working together in the critical area of technology transfer, the process of converting research findings into applied clinical practices. It has recently been noted that in the United States, cardiovascular biomedical engineering advances are in need of rapid and widespread application. It is essential that the scientific community, the industrial manufacturers of drugs and biomedical equipment, the community of practicing health professionals and the whole range of health care planners and administrators rapidly learn about and apply the most recent and effective biomedical technology. The Cardiovascular Biomedical Engineering Working Group includes representatives of 13 Federal agencies engaged in scientific investigations, regulation, professional education, health planning, health financing, public education, and the actual delivery of certain health services.

This working group's most recent deliberations occurred on-site at the EPA-supported National Environmental Research Center Human Studies Laboratory. Working group members observed this unique and highly sophisticated human exposure facility to determine its potential significance for their agencies' programs. As a result, plans are being made whereby the laboratory may be utilized by other Federal agencies for testing cardiopulmonary effects of ambient levels of airborne pollutants. This kind of interaction facilitates the timely exchange of information between developers, users and regulators, and enhances the transfer of technology.

Nutrient Composition of Foods Working Group

The Working Group on Nutrient Composition of Foods has drawn together individuals who are actively involved in diverse Federal programs for which an accurate knowledge of the nutrient composition of foods has significance. Food composition data are required for research, patient education, food purchasing for hospital food services, public education, and food labeling. Reliable data are needed regarding the positive and negative effects of diet on health in order to convince people to modify their diets to avoid the danger of current practices or to realize the benefits of different dietary patterns.

The membership of the group is drawn from experts in the fields of cardiovascular and public health nutrition, lipidology, cardiology, food composition, food chemistry, food technology and nutrition data base systems. As a result of the group's deliberations, a list of cardiovascular priorities for analyzing the nutrient composition of foods has been developed. This is especially important in light of an ongoing USDA/NHLBI collaborative effort to obtain analyses of the nutrient composition of common American foods. The USDA laboratory has the capability for high-quality quantitative analysis of nutrient composition. Recently the USDA asked the group for guidance in selecting the most appropriate foods for analysis, especially as they relate to cardiovascular diseases. The group is providing this guidance not only in the ranking of foods for analysis, but also by providing data on the analyses already performed by member organizations, data on the quantity and frequency with which Americans consume certain foods, and data on technological capability and feasibility of performing analyses of those nutrients specifically related to cardiovascular disease.

Program Impact Analysis (PIA) Working Group

Analyzing and assessing program impact are crucial to planning, refining, and implementing the National Program. At present, a large number of Federal agencies are conducting evaluation studies and collecting data concerning the impact and outcomes of their program activities. A range of methodologies and data bases has been developed. NHLBI recognizes that the methods, expertise, and information developed in these efforts may be adaptable to the analysis of heart, lung, and blood programs and can add significantly to NHLBI's own expertise in program assessment. In response, the IATC has recently organized a Categorical Working Group to share information, experience, and methods concerning program assessment.

The PIA working group has representatives from a wide range of governmental agencies including users, regulators, and providers of health services. The group's purpose is to share experience, knowledge, and approaches to program assessment, with special reference to heart, lung, and blood programs. Recently the group has conducted seminars on the development and application of evaluation methodologies. One seminar focused on the use of the time series method for program assessment. The Department of Transportation has applied and refined this method to assess the effect of the 55-mile-per-hour speed limit as well as the effect of DOT's Alcohol Safety Action Program. By using this method, DOT has been able to determine program outcomes which would not have been possible to observe otherwise. Through discussions in the working group, NHLBI has identified opportunities to apply time series methods in its own program evaluations. The method will be used in NHLBI's evaluation of the impact of nutrition education programs on consumer food purchases.

Another seminar focused on the measurement of research advance using bibliometric techniques. This method has been fairly regularly applied to biomedical research programs and NHLBI is currently employing the technique in its evaluation of progress in hypertension and pulmonary research. Other agencies have expressed considerable interest in the technique, and recent working group deliberations have identified a number of program areas of other Federal agencies where the bibliometric techniques could be applied to measure progress. Thus, the outcomes of the PIA activities to date have yielded tangible benefits for both NHLBI efforts and those of other participating organizations.

PARTICIPATION IN COLLABORATIVE EFFORTS SPONSORED BY OTHER ORGANIZATIONS

Another aspect of program coordination involves the utilization of NHLBI scientists and administrators in the development of health planning policies in areas that could have an impact upon heart, lung, and blood diseases. One such area relates to the impact upon health of worsening environmental quality due to increasing demand for the development of new energy resources. NHLBI works in conjunction with the Environmental Protection

Agency and the Department of Energy to address potential health problems in advance of any policy decisions which will affect the Nation's health. NHLBI also works in a comparable manner with the National Science Foundation, ad hoc task forces, and other appropriate Federal organizations. A few of these committees and task forces are described below.

Toxic Substance Strategy Committee

NHLBI actively participates in the Toxic Substance Strategy Committee, charged by the President in his 1977 environment message to develop an interagency program to eliminate "overlaps and gaps" and to "coordinate Federal research and regulatory activities" affecting toxic substances. As part of the work program of the Committee, an assessment of Federal research and development activities, entitled "Toxic Substances: A Review of Federal Research Development," has been completed. Among other matters the Committee has studied the scope of toxic substances research being supported by the Federal government and how these research activities are being coordinated. The Committee has deliberated and made recommendations concerning what future research is needed, how the research should be monitored and evaluated, and what personnel needs will be to conduct the needed research. Special emphasis has once again been placed on mechanisms for technology transfer and the most effective methods for disseminating research findings to those who use them in practice.

Public Health Service Working Group on Health Effects of Energy Technology

NHBLI is an active member of the Public Health Service Working Group on Health Effects of Energy Technology. This committee is charged to assess the state of the science in areas related to possible negative health and environmental effects of existing and new technology (e.g., respiratory effects of pollutants of coal gasification and liquefaction). In this endeavor, NHLBI provides information on the effect of energy-related contaminants on the cardiovascular and respiratory systems.

Management and Logistics of Blood Banking

In a number of instances, NHLBI jointly sponsors scientific conferences and working groups in cooperation with other organizations. One such undertaking is the recent National Conference on the Management and Logistics of Blood Banking. This was a joint endeavor sponsored by the American Blood Commission and NHLBI. It brought together directors of transfusion services, cost review experts, economic analysts, medical educators, legal and insurance experts, scientists, industrialists, labor union representatives and many representatives of voluntary and other private health organizations. The conference has published abstracts and articles on subjects ranging from the economics of blood services to continuing laboratory education, from liability insurance issues to regulatory and health planning problems, from quality control to cooperative endeavors of medical schools and the hundreds of affiliated hospitals that work together in regionalized systems.

PLANNING AND ASSESSMENT TASK FORCES AND ADVISORY GROUPS

In many instances it is essential for NHLBI to gain the input of a wide range of scientific expertise in order to determine future directions for heart, lung, and blood diseases research. A specific mechanism chosen for this purpose is formation of task forces and advisory groups. Invariably these involve scientists supported by other Federal agencies as well as program staff from those agencies. Two examples of recent efforts follow.

Juvenile-Onset Diabetes — Assessment of Treatment

In response to a recommendation of the National Commission on Diabetes, the NHLBI and the National Institute of Arthritis, Metabolism, and Digestive Diseases have formed a consultant/advisory group on efficacy of control of blood glucose in the development of the vascular complication in diabetes. This group is assisting the two institutes to develop a controlled clinical trial to evaluate the effects of different methods of controlling juvenile-onset diabetes upon the development of vascular complications of diabetes. Close collaborative relationships are being maintained among the NHLBI, NIAMDD, the American Diabetes Association, and the Juvenile Diabetes Foundation.

Evaluation of Progress in Arteriosclerosis Research

The Task Force on Arteriosclerosis made recommendations in 1971 which have formed the basis of the NHLBI Arteriosclerosis Program since then. It

has been recommended that these 1971 recommendations be systematically updated to assess current and future needs. In response to this problem, NHLBI has continued the efforts of the Working Group on Arteriosclerosis. This group has a very broad and critical mandate. It is constituted to undertake an assessment of arteriosclerosis from its basic processes to the diagnosis, treatment and rehabilitation associated with its clinical manifestations. The Institute's responsibilities in this area have been extended beyond research and clinical trials to include the translation and application of research findings through demonstration and education programs. Thus the working group must be broadly constituted, including representatives from multiple disciplines ranging from molecular biology to health education, from biochemistry to epidemiology, from clinicians to sociologists.

Recent meetings of the working group have provided for input from a wide range of Federal agencies whose activities are related to NHLBI arteriosclerosis concerns. The Office on Smoking and Health has provided much useful information concerning forthcoming publications, public education activities, and several technical issues concerning the relationship between cigarette smoking and arteriosclerosis risk factors. The National Institute of Arthritis, Metabolism, and Digestive Diseases has provided important information concerning the relationship between diabetes and arteriosclerosis as well as sharing preliminary results of NIAMDD's current state-of-the-art assessment of research needs in carbohydrate and lipid metabolism. The Center for Disease Control has assisted in the area of laboratory quality control and standardization of lipid analyses. Excellent standardization between the Institute's laboratory and the NHLBI's Lipid Research Centers has been achieved because the laboratory has been involved in both the planning and implementation of lipid analyses. The Department of Agriculture, too, has assisted in the area of nutrient analyses, particularly in defining the state of development of nutrient analysis methodology and the state of knowledge of nutrient composition.

It is only through these complex interchanges that the difficult task of coordination can be accomplished. The mechanisms used must be as varied as the tasks are specific; yet the overall result must be a growing integration, synthesis and application of scientific knowledge. No single mechanism or individual example can possibly describe the entire process or even begin to illustrate the commitment which NHLBI has made toward attaining a productive and cohesive national program. But it is exciting to realize that out of this complex framework, scientific knowledge is developed and utilized and a whole art of disease prevention and control continues to unfold.

X.
International Activities

Problems in cardiovascular, lung and blood diseases, and blood resources are international and interrelated. In response, the NHLBI has significantly expanded its international activities and contacts over the past few years through informal exchange of information between scientists from the United States and other countries and also more formal arrangements with scientists and institutions in other lands.

U.S.-U.S.S.R. EXCHANGE PROGRAM

The largest and most diversified of NHLBI's formal international programs, the U.S.-U.S.S.R. Health Exchange Program, began formally in 1972 and was renewed in 1977, for 5 years. Ongoing cooperation is carried out under two agreements, the first one in Medical Science and Public Health and the second one in Artificial Heart Research and Development. The first agreement also includes research in cancer and environmental health as well as several other areas. Seven cardiovascular programs are currently conducted under this agreement. These are:

- Pathogenesis of Arteriosclerosis
- Management of Ischemic Heart Disease
- Myocardial Metabolism
- Congenital Heart Disease
- Sudden Death
- Blood Transfusion, Blood Components, and Prevention of Hepatitis with Particular Reference to Cardiovascular Surgery
- Hypertension Etiology, Treatment, and Prevention.

Arteriosclerosis, the most common cause of cardiovascular disease in the U.S. and U.S.S.R., is directly or indirectly responsible for more deaths than any other disease in these two nations. A joint study is determining the prevalence of hyperlipidemias and ischemic heart disease and also exploring the role of

diet as a potential risk factor. The U.S.-U.S.S.R. study involves men between 40 and 59 years old; and it is hoped that by identifying men with hyperlipidemia, by testing for the presence of ischemic heart disease, and by surveying for cardiovascular risk factors, the vital link between elevated blood fats and arteriosclerosis will be further elucidated.

In the area of ischemic heart disease, Soviet and U.S. scientists are systematically assessing and comparing the manner in which patients with ischemic coronary heart disease are treated by various pharmacologic and surgical procedures in the two countries.

With respect to myocardial metabolism, a fundamental understanding of the structure and function of the heart muscle is crucial to improving methods of prevention and therapy. Collaborative efforts have resulted in the exchange of biochemical and physiological data on healthy and diseased heart muscle.

The objectives of the U.S.-U.S.S.R. exchanges in study of congenital heart disease are to explore new diagnostic methods and postoperative care procedures and also to study ways to improve the surgical treatment of complex heart defects.

Sudden death from coronary arteriosclerosis may occur in patients with chest pain and with a history of heart attacks; however, it may also occur in individuals with no previous symptoms of heart disease. The immediate mechanism of sudden death is believed to be a disturbance in the heart's rhythm, and the role of arrhythmias in sudden death is one of the most important problems in cardiology. U.S. and Soviet scientists have held extensive discussions on the magnitude of the problem in their respective countries, the relationship between arrhythmias and sudden death, monitoring techniques, and emergency treatment.

Hypertension is one of the major health problems in the world, in terms of both its prevalence and its impact. It is estimated that about 35 million Americans (1 in 6) have definite high blood pressure (160/95 or higher) and are at significant risk for future cardiovascular, cerebrovascular, and renal disease. The hypertension problem in the U.S.S.R. is also a serious one. The First Joint U.S.-U.S.S.R. Symposium in Hypertension was held in June 1978, in Sochi, U.S.S.R.

In addition to cooperating in the seven program areas of arteriosclerosis, ischemic heart disease, myocardial metabolism, congenital heart disease, sudden death, blood management, and hypertension, scientists from the U.S. and the U.S.S.R. have jointly explored artificial heart research and development. They have shared research data on components of the circulatory support system. International teams of scientists have implanted calves with artificial hearts, and prototype, implantable artificial hearts with external drive units have been exchanged between the United States and the Soviet Union.

International symposia and working sessions have been held at regular intervals throughout the past 6 years to discuss the major problem areas. The results from these symposia have been published in both English and Russian, and further publications are planned in the coming year. In addition, delegations of senior scientists from the U.S. and U.S.S.R. have visited their counterpart institutions, and both countries have exchanged research scientists to cooperate on a number of joint research projects.

COOPERATIVE PROGRAMS WITH OTHER NATIONS

Among the formal and informal NHLBI programs currently in existence or being developed with other countries are the following cooperative efforts:

- Canada — Lipid research
- Federal Republic of Germany — Atherosclerosis and hypertension
- France — Basic reactions of pulmonary tissues to inhaled pollutants
- Israel — Lipid research
- Italy — Heart disease prevention, focusing on hyperlipidemia-nutrition, smoking and hypertension
- Japan — Epidemiological studies of coronary heart disease

- Poland — Prevention of coronary heart disease
- Spain — Biochemistry and epidemiology related to NHLBI research areas
- Yugoslavia — Epidemiology of cardiovascular diseases and etiologic and risk factors in respiratory disease.

The NHLBI has also been instrumental in developing an international computer-based chemical information system. This on-line system, begun by NHLBI and the EPA, has now become an interagency, international system linking NIH, EPA, the National Bureau of Standards of the Department of Commerce, the Department of Energy, and the Food and Drug Administration. International contributors include Great Britain, the Netherlands, West Germany, Switzerland, Japan, Hungary, France, Finland, and Sweden. Computer access, through an international satellite, enables scientists worldwide to obtain essentially instantaneous responses via computer terminals in their own laboratories.

Institute Director Dr. Robert I. Levy (fourth from right) meets with a delegation from the People's Republic of China.

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